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Proceedings of the Conference on Non-Hodgkin's Lymphomas

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Begin the article with a short summary.

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Contents

Cancer Treatment Reports
Vol. 61, No. 6
September 1977

Page

Proceedings of the Conference on Non-Hodgkin's Lymphomas (San Francisco, California, September 30–October 2, 1976)

Rappaport Classification of Non-Hodgkin's Lymphoma: Histologic Features and Clinical Significance 935
Gerald E. Byrne, Jr
University of Miami School of Medicine, Florida

Pathology of the Non-Hodgkin's Lymphomas: New Classifications 945
Ronald F. Dorfman
Stanford University Medical Center, California

Functional Markers: A New Perspective on Malignant Lymphomas 953
Elaine S. Jaffe, Raul C. Braylan, Koji Nanba, Michael M. Frank, and Costan W. Berard
National Cancer Institute, Bethesda, Maryland

Prognostic Significance of Lymphocytic Surface Markers and Histology in Adult Non-Hodgkin's Lymphoma 963
Clara D. Bloomfield, John H. Kersey, Richard D. Brunning, and Kazimiera J. Gajl-Peczalska
University of Minnesota Hospitals, Minneapolis

Lukes-Collins Classification and Its Significance 971
Robert J. Lukes and Robert D. Collins
University of Southern California School of Medicine, Los Angeles

Clinical and Surgical (Laparotomy) Evaluation of Patients With Non-Hodgkin's Lymphomas 981
Don R. Goffinet, Roger Warnke, N. R. Dunnick, Ronald Castellino, Eli Glatstein, Thomas S. Nelsen, Ronald F. Dorfman, Saul A. Rosenberg, and Henry S. Kaplan
Stanford University Medical School, California

Sequential Staging in Non-Hodgkin's Lymphoma 993
Bruce A. Chabner, Ralph E. Johnson, Vincent T. DeVita, George P. Canellos, Susan P. Hubbard, Sandra K. Johnson, and Robert C. Young
National Cancer Institute, Bethesda, Maryland

Comparison of Nodal Primary Versus Extranodal Primary Histiocytic Lymphoma 999
Kenneth R. Hande, Ronald R. Reimer, and Richard I. Fisher
National Cancer Institute, Bethesda, Maryland

Page

Role of Staging in Childhood Non-Hodgkin's Lymphoma 1001
Norman Jaffe, Donald Buell, J. Robert Cassady, Demetrius Traggis, and Howard Weinstein
Sidney Farber Cancer Institute, Boston, Massachusetts

Systematic Re-Staging in the Management of Non-Hodgkin's Lymphomas 1009
Terence S. Herman and Stephen E. Jones for the Southwest Oncology Group
University of Arizona Health Sciences Center, Tucson

Peritoneoscopy: A Technique to Evaluate Therapeutic Efficacy in Non-Hodgkin's Lymphoma Patients 1017
Tom Anderson, Richard A. Bender, Stephen H. Rosenoff, Harmar D. Brereton, Bruce A. Chabner, Vincent T. DeVita, Susan P. Hubbard, and Robert C. Young
National Cancer Institute, Bethesda, Maryland

Validity of the Ann Arbor Staging Classification for the Non-Hodgkin's Lymphomas 1023
Saul A. Rosenberg
Stanford University School of Medicine, California

Discussion I 1029
Saul A. Rosenberg (Chairman)

Discussion II: Roundtable Discussion of Histopathologic Classification 1037
Costan W. Berard (Chairman)

Chemotherapy of the Non-Hodgkin's Lymphomas: The Stanford Experience 1049
Carol S. Portlock and Saul A. Rosenberg
Stanford University Medical Center, California

Combination Chemotherapy in Non-Hodgkin's Lymphoma: Results of Long-Term Followup 1057
Tom Anderson, Richard A. Bender, Richard I. Fisher, Vincent T. DeVita, Bruce A. Chabner, Costan W. Berard, Larry Norton, and Robert C. Young
National Cancer Institute, Bethesda, Maryland

Chemotherapy of Non-Hodgkin's Lymphoma: 10 Years' Experience in the Southwest Oncology Group 1067
Charles A. Coltman, Jr, James K. Luce, Eugene M. McKelvey, Stephen E. Jones, and Thomas E. Moon
Southwest Oncology Group

Chemotherapy of Non-Hodgkin's Lymphomas: Eastern Cooperative Oncology Group Experience 1079
John M. Bennett, Raymond E. Lenhard, Jr, Ediz Ezdinli, Gerhard J. Johnson, Paul P. Carbone, and Stuart J. Pocock
Eastern Cooperative Oncology Group

Page

BCNU With and Without Cyclophosphamide, Vincristine, and Prednisone (COP) and Cycle-Active Therapy in Non-Hodgkin's Lymphoma 1085
John R. Durant, Richard A. Gams, Alfred A. Bartolucci, and Ronald F. Dorfman
University of Alabama, Birmingham

Overview of Four Clinical Studies of Chemotherapy for Stage III and IV Non-Hodgkin's Lymphomas by the Cancer and Leukemia Group B 1097
Nis I. Nissen, Thomas Pajak, Oliver Glidewell, Hans Blom, Michael Flaherty, Donald Hayes, Ross McIntyre, and James F. Holland
Cancer and Leukemia Group B

Combination Therapy for Diffuse Histiocytic Lymphoma That Includes Antimetabolites 1109
E. Cadman, L. Farber, D. Berd, and J. Bertino
Yale University School of Medicine, New Haven, Connecticut

Non-Cross-Resistant Combinations in Stage IV Non-Hodgkin's Lymphomas 1117
Gianni Bonadonna, Silvio Monfardini, and Eugenio Villa
Istituto Nazionale Tumori, Milan, Italy

Discussion III: Chemotherapy of the Non-Hodgkin's Lymphomas 1125
Emil Frei III (Chairman)

Radiation Therapy of Localized Non-Hodgkin's Lymphoma 1129
R. S. Bush, M. Gospodarowicz, J. Sturgeon, and R. Alison
Ontario Cancer Institute, Toronto, Canada

Team Approach to Management of Non-Hodgkin's Lymphomas: Past and Present 1137
Lillian M. Fuller, Jess F. Gamble, James J. Butler, Joseph G. Sinkovics, Sidney Wallace, Richard G. Martin, Edmund A. Gehan, and C. C. Shullenberger
The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston

Total-Body Irradiation in the Treatment of Lymphocytic Lymphoma 1149
John T. Chaffey, Samuel Hellman, David S. Rosenthal, and William C. Moloney
Joint Center for Radiation Therapy, Boston, Massachusetts

Advanced Lymphocytic Lymphoma: Randomized Comparisons of Chemotherapy and Radiotherapy, Alone or in Combination 1153
Robert C. Young, Ralph E. Johnson, George P. Canellos, Bruce A. Chabner, Harmar D. Brereton, Costan W. Berard, and Vincent T. DeVita
National Cancer Institute, Bethesda, Maryland

Management of Childhood Non-Hodgkin's Lymphoma 1161
Sharon B. Murphy
St. Jude Children's Research Hospital, Memphis, Tennessee

Page

Discussion IV: Other Treatment of the Non-Hodgkin's Lymphomas 1175
Samuel Hellman (Chairman)

Immunologic Classification of Non-Hodgkin's Lymphomas: Current Status 1179
Maxime Seligmann, Jean-Claude Brouet, and Jean-Louis Preud'homme
Research Institute on Blood Diseases, Hopital Saint-Louis, Paris, France

Curability of Non-Hodgkin's Lymphomas 1185
Eugene M. McKelvey and Thomas E. Moon
The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston

Current Cooperative Clinical Trials in the Non-Hodgkin's Lymphomas 1191
F. M. Muggia, H. L. Davis, Jr, and M. Rozencweig
National Cancer Institute, Bethesda, Maryland

Combined Modality Therapy in Malignant Lymphomas 1199
Eli Glatstein, Sarah S. Donaldson, Saul A. Rosenberg, and Henry S. Kaplan
Stanford University Medical Center, California

New Approaches to the Treatment of Non-Hodgkin's Lymphoma 1209
Emil Frei III, Stuart Schlossman, and Mervyn Israel
Sidney Farber Cancer Institute, Boston, Massachusetts

Discussion V: Overview of the Non-Hodgkin's Lymphomas 1219
Vincent T. DeVita (Chairman)

Summary of Symposium 1223
Vincent T. DeVita
National Cancer Institute, Bethesda, Maryland

ANNOUNCEMENTS 1229

Seminar on Malignant Bone Tumors
Seminars in Oncology at Roswell Park Memorial Institute
US National Committee for the International Union Against Cancer Travel Awards
Change in Training Requirements for the American Board of Internal Medicine's Subspecialty Examinations
Postgraduate Course in Neuro-Oncology

The Secretary of Health, Education, and Welfare has determined that the publication of this periodical is necessary in the transaction of the public business required by law of this Department. Use of funds for printing this periodical has been approved by the Director of the Office of Management and Budget through January 31, 1980.

Proceedings of the Conference on Non-Hodgkin's Lymphomas

Cancer Clinical Investigation Review Committee
National Cancer Institute

Editors: Stephen E. Jones
John Godden

September 30 to October 2, 1976
San Francisco, California

NOTICE

A limited number of copies of this issue of *Cancer Treatment Reports* on the non-Hodgkin's lymphomas are available. Please contact Dr. Stephen E. Jones, Section of Hematology-Medical Oncology, University of Arizona Health Sciences Center, Tucson, Ariz 85724.

Editor's Note

Between September 30 and October 2, 1976, in San Francisco, California, the Cancer Clinical Investigation Review Committee of the National Cancer Institute sponsored a symposium to review the state-of-the-art for malignant lymphomas other than Hodgkin's disease (the non-Hodgkin's lymphomas or NHL). The program planning committee consisted of myself as chairman, Dr. Saul Rosenberg (medical oncology), Dr. Samuel Hellman (radiation oncology), and Dr. Robert Lukes (pathology).

Our intent in arranging the final program was to invite a limited number of investigators to review available information on pathology, staging, treatment, and prognosis, to survey the majority of current clinical trials, and to define (but not resolve) some of the current controversies relating to NHL.

Each of the five major sessions of the symposium was followed by a discussion period, and edited versions of these discussions along with manuscripts from each of the participants form the content of this issue. Most of the material presented herein is either new or substantially up-dated from previous publications. Although I hope the entire issue is read with care, I would draw your attention to the experience with laparotomy in these diseases (Dr. Goffinet et al), the pathology round-table discussions led by Dr. Henry Rappaport, the use of restaging in evaluating therapeutic response (Dr. Herman et al), the summaries of the four major cooperative group programs, the paper on management of childhood lymphoma by Dr. Murphy, the thoughtful critique of applying immunologic methods to the study of these tumors by Dr. Seligmann, and finally, the succinct summary of the meeting with its implications for current practical patient management by Dr. DeVita. All of the information from this symposium should serve oncologists as a basis upon which improved treatment programs can be devised.

Finally, I wish to express my thanks to the many individuals who were responsible for the successful conduct of the meeting and the subsequent publication of this issue. Ms. Suzanne McCoy, Joanne Yanez, and Margo Walter from the University of Arizona were immeasurably helpful. John Godden, MD, served as co-editor and was primarily responsible for the editing of this issue. Essential grant support was provided by the National Cancer Institute (CA-19892).

Stephen E. Jones

University of Arizona Health Sciences Center
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Rappaport Classification of Non-Hodgkin's Lymphoma: Histologic Features and Clinical Significance[1]

Gerald E. Byrne, Jr[2,*]

SUMMARY

The architectural arrangement of the neoplastic cells and their cytologic identification form the histologic basis of the Rappaport classification of non-Hodgkin's lymphoma. Clinical studies have shown the favorable prognosis of the nodular lymphomas while the diffuse lymphomas irrespective of cell type have a poor prognosis. Several recent studies have shown that pathologists can identify the nodular and diffuse patterns with a high degree of reproducibility. The cytologic subclassification has, however, not achieved a similar high degree of reproducibility. The Southwest Oncology Group study has shown the most reproducible subgroups to be the nodular poorly differentiated lymphocytic malignant lymphoma (ML) and the diffuse histiocytic ML. The clinical significance of the Rappaport classification when applied to childhood lymphomas is not as clear as in adult lymphomas. In view of the recent description of a new clinicopathologic entity primarily in children and adolescents (ie, lymphoblastic ML), it is apparent that the childhood lymphomas will have to be examined more critically in order to determine the clinical significance of this classification. Although some have proposed new classifications of these lymphomas based upon immunologic identification of cell origin, none have been shown to be of clinical significance. Based on recent immunologic and clinical studies, a modified classification of the non-Hodgkin's lymphoma is proposed which does not alter its clinical usefulness.

[Cancer Treat Rep 61:935–944, 1977]

Recently, both clinicians and pathologists have directed special attention towards the non-Hodgkin's lymphomas. Histologic material derived from staging laparotomy has provided the pathologist with an opportunity to determine accurately the distribution of disease in the various types of non-Hodgkin's lymphoma (1–5). The availability of such material has also allowed us to apply new techniques to the study of these disorders in order to determine the origin of the cells in these lymphomas (6,7). With the acquisition of such knowledge, efforts have been made by some to improve the histologic classification of the non-Hodgkin's lymphomas by adopting terminology which biologically is more accurate (8–10). Other investigators have chosen to adopt a terminology that does not incorporate specific reference to cytogenesis and to wait for the results of additional studies (11,12).

This proliferation of new classifications in a complex area of pathology and the confusion it engenders prompt the following question: What conditions must be met in order to produce an acceptable morphologic classification of non-Hodgkin's lymphoma? I would suggest that, to be considered acceptable, such a classification must (*a*) provide the clinician with information that is clinically significant; (*b*) be based upon morphologic criteria which are sufficiently distinctive that, when applied by those who are not expert, they will be highly reproducible when compared with expert interpretations; and (*c*) be accurate and valid scientifically.

Many clinical studies have shown that the Rappaport classification of non-Hodgkin's lymphomas has clinical relevance (1) and, although this scheme

[1]Supported by Public Health Service grant CA-19892 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

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is undergoing critical evaluation, it remains the only current morphologic classification that has such relevance. Few morphologic classifications have been evaluated critically so as to determine whether the histologic features which are the basis for their interpretation can be applied in a reliable and reproducible manner. The present paper will offer data concerning the reproducibility of the histologic features of the Rappaport classification.[3] Studies of reproducibility may be placed in jeopardy by many factors, the most important of which are the biopsy technique and the technical preparation of the specimen. Good reproducibility calls for care from the moment lymph node biopsy is considered. The surgeon should select the best biopsy site and should, if possible, remove a large lymph node and take care not to fragment it. The specimen, preferably unfixed, must be delivered promptly to the pathologist who will prepare the tissues for adequate fixation. His technical staff must be skilled in the preparation of thin, well-stained, histologic specimens. Unfortunately, these conditions are not always fulfilled, and thus it is impossible to make a reliable interpretation of many histologic specimens.

[3]Byrne GE, Jr, Coppleson LW, and Rappaport H. Unpublished observations.

Because the data in this paper constitute the first assessment of the histologic reproducibility of a morphologic classification of non-Hodgkin's lymphoma, it is difficult to decide whether the reproducibility achieved here has reached acceptable levels. However, this study does indicate the state of the art and it does indicate those morphologic features which can be reliably applied by pathologists in general and those which can be applied with confidence only by pathologists with special experience in lymphomas.

Thus, it is the purpose of this paper to discuss the morphologic basis of the Rappaport classification and its reproducibility, to point out those areas which are difficult to interpret, and to specify where the classification must be modified for future use.

THE RAPPAPORT CLASSIFICATION

The Rappaport classification of non-Hodgkin's lymphomas is based upon two morphologic features: the overall geographic pattern of the lymph node and the cytologic characteristics of the lymphoma cell population (13,14). In malignant lymphomas (ML) with a nodular pattern (fig 1) the cells are arranged in regular nodules which are distributed throughout the lymph node and efface its normal architecture. In most cases the abnormal cells are

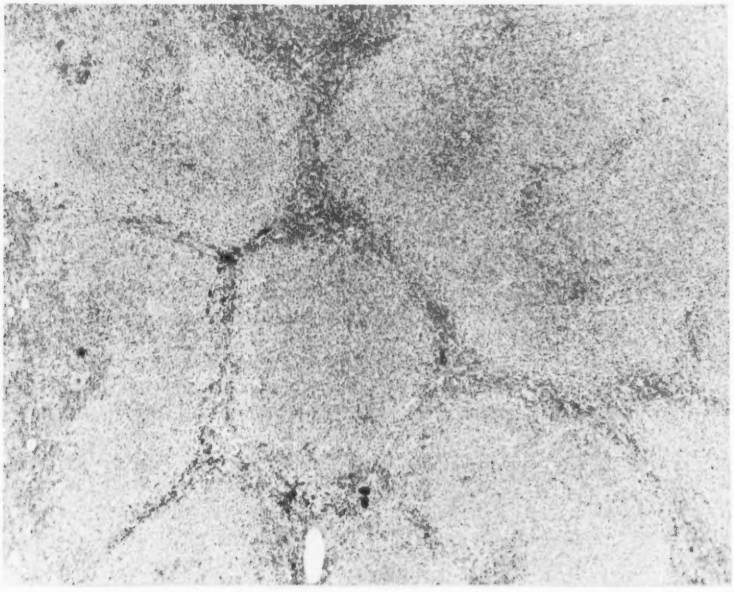

FIGURE 1.—Nodular pattern. Regularly shaped nodules distributed throughout cortex and medulla of lymph node. (H & E stain, × 45.)

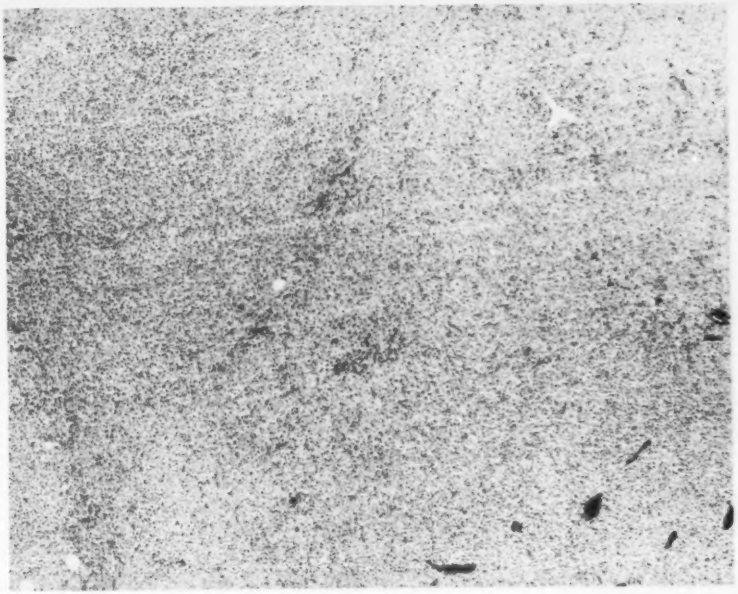

FIGURE 2.—Diffuse lymphoma. There is no nodular aggregation of the lymphoma cells in this diffuse lymphoma. The cells are distributed throughout the lymph node replacing the normal lymph node components. (H & E stain, × 45.)

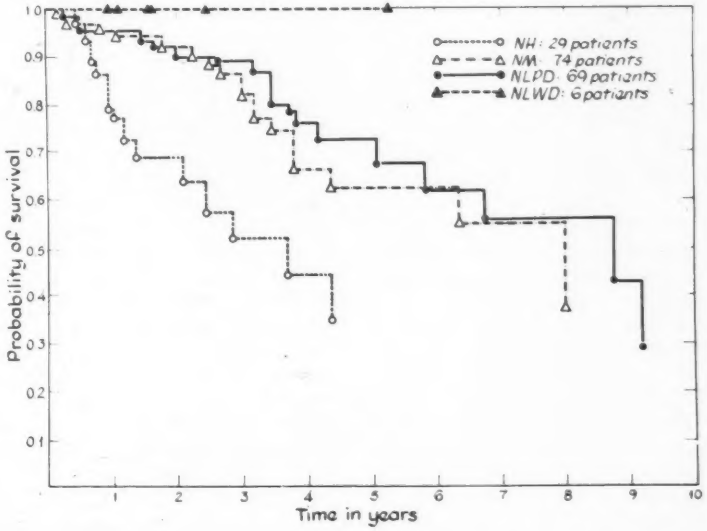

FIGURE 3.—Nodular lymphomas. Actuarial survival for patients with each histologic subtype. NH = nodular histiocytic, NM = nodular mixed, NLPD = nodular lymphocytic poorly differentiated, NLWD = nodular lymphoma well differentiated. (Reprinted with permission from Cancer 31:816, 1973.)

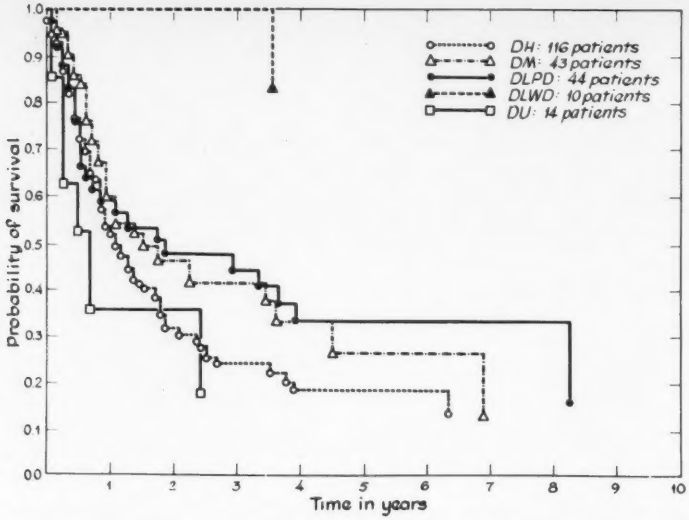

FIGURE 4.—Diffuse lymphomas. Actuarial survival for patients with each histologic subtype. (Reprinted with permission from Cancer 31:816, 1973.)

limited to the nodule while in other cases the abnormal cells may also be found between the nodules. In MLs with a diffuse pattern (fig 2) there is no aggregation of cells into nodules; rather, they are distributed throughout the lymph node and this process effaces its normal architecture. Therefore, the Rappaport classification made its first contribution when it divided the non-Hodgkin's lymphomas into nodular and diffuse groups. Clinical studies have shown a marked difference in survival between these groups (1). The nodular type (fig 3), irrespective of the cell type of which it is composed, carries a better prognosis than the diffuse type (fig 4).

The reproducibility of these histologic features, ie, nodularity versus diffuseness, was studied during an evaluation of the reliability of histologic criteria at a conference held at the University of Chicago in 1973.[3] As part of this study, a group of 24 pathologists evaluated 91 cases of non-Hodgkin's lymphoma using as a standard the majority diagnosis of the members of the Lymphoma Pathology Panel (LPP) (15). The panel determined that 32 of these 91 cases had a nodular pattern and 59 had a diffuse pattern. The pathologists participating in the conference correctly identified a nodular pattern in 83% of the cases and incorrectly ruled that 5% of the cases were diffuse. Twelve percent of these cases were identified by the pathologists to have both a nodular and diffuse pattern. The LPP members identified these cases and had included them under the group designated as nodular. Thus, the conference pathologists identified the nodular histologic pattern in 95% of the cases. Recently, data concerning reproducibility have been published by the Southwest Oncology Group (SWOG) (16). In this study, histologic material from registered patients on SWOG clinical trials was submitted to a member of the LPP by the pathologists of the participating institutions. There was agreement in 91% of the 69 cases identified as having a nodular histologic pattern by the institutional pathologists.

The diagnosis of diffuse lymphoma was made with a high degree of reliability in the University of Chicago study. The panel considered 59 cases to be diffuse lymphomas and the pathologists correctly identified this pattern in 93% of the cases. They incorrectly applied the term "nodular" to only 4% of the specimens. Again, the pathologists recognized minimal nodularity in 3% of the cases and cautiously identified these specimens as having both patterns. Thus, a diffuse pattern was identified in 96% of these cases. In the SWOG study, the institutional pathologists applied correctly the diagnosis of diffuse lymphoma to 80% of the specimens considered by the consultants to have a diffuse pattern (16).

The second major parameter in the Rappaport classification is the cytology of the lymphoma. Evaluation of cell morphology considers such features

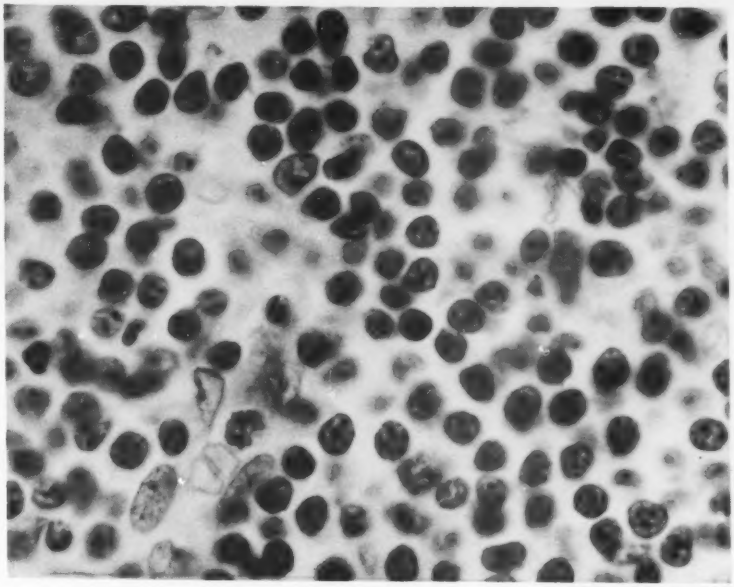

FIGURE 5.—Cytology of well-differentiated lymphocytic lymphoma. Monotonous population of small cells with round and regular nuclei. (H & E stain, × 1100.)

as nuclear size, configuration, and the monotony or heterogeneity of the cell population. We use the nucleus of the tissue histiocyte or endothelial cell as a reference when evaluating cell size. If the nuclei of the cells of either a nodular or diffuse lymphoma are smaller than the nuclei of the histiocyte or endothelial cell, these cells would be considered well-differentiated or poorly differentiated lymphocytes in this classification. The next feature to evaluate would be the nuclear configuration. If the nuclei are small, round, and regular, the cells are considered to be well-differentiated lymphocytes (fig 5). If the nuclei are small, indented, and irregular, the cells are considered to be poorly differentiated lymphocytes (fig 6). MLs composed of cells with nuclei that are as large as or larger than the nucleus of the tissue histiocyte or endothelial cell would be called either ML-histiocytic (fig 7) or ML-undifferentiated of the Burkitt or non-Burkitt types. MLs composed of a heterogenous population of cells, some with nuclei that are as large as or larger than endothelial cells and others with small, irregular, and indented nuclei, are designated ML-mixed (lymphocytic and histiocytic type) (fig 8).

Thus, the Rappaport classification contains five major cytologic groups. These include: (*a*) well-differentiated lymphocytic; (*b*) poorly differentiated lymphocytic; (*c*) mixed (lymphocytic and histiocytic); (*d*) histiocytic; and (*e*) undifferentiated (Burkitt and non-Burkitt). With the exceptions of the ML-well-differentiated lymphocyte type and the ML-undifferentiated type, these cytologic groups may present with either a nodular or a diffuse pattern. There is disagreement as to whether the ML-well-differentiated lymphocytic type ever presents with a nodular pattern (3,4). Pangalis et al (17), for example, recently reported a series of 108 patients who had a lymph node cytology that was ML-well-differentiated lymphocytic, and only two of these had a nodular pattern. Only the diffuse pattern has been observed in the ML-undifferentiated type.

Does this cytologic subclassification have clinical significance? Jones et al (1) have demonstrated differences in survival between the various types of nodular lymphomas (fig 3). However, except for the ML-well-differentiated lymphocytic type, all patients with diffuse lymphomas have a poor prognosis (fig 4).

The reproducibility of a cytologic subclassification of the non-Hodgkin's lymphomas was considered during the University of Chicago conference when a group of non-Hodgkin's lymphomas were so classified.[4] Ninety-one cases were subclassified by the pathologists and their results were compared to

[4]*See* footnote 3.

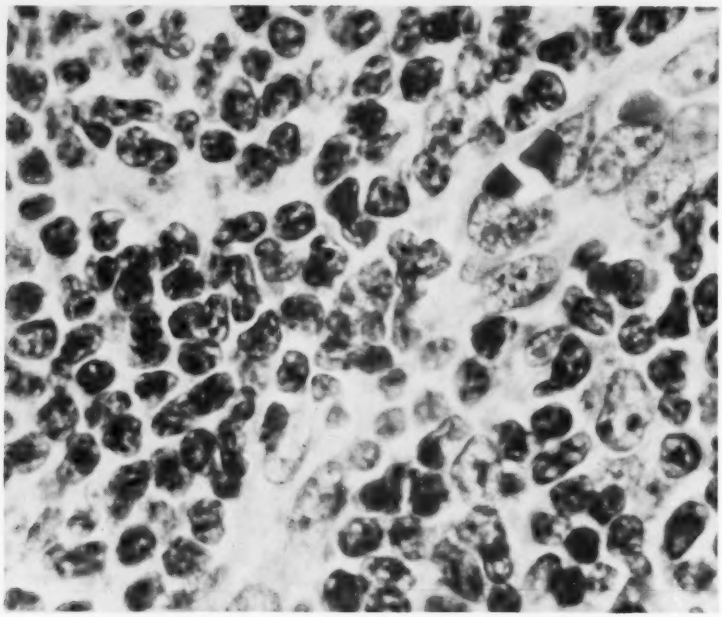

FIGURE 6.—Cytology of poorly differentiated lymphocytic lymphoma. Monotonous population of small cells with irregular and indented nuclei. (H & E stain, × 1100.)

those of the LPP (15). The percent agreement (table 1) provides an indication of the reproducibility of the cytologic subclassification. The greatest agreement was in the group designated as ML-histiocytic type and the poorest was in the group considered to be ML-undifferentiated type.

Relatively poor agreement in the group identified as ML-undifferentiated is not surprising because the World Health Organization (WHO) study group has indicated that the diagnosis of ML-undifferentiated Burkitt's type could not be reliably established using only sections stained with hematoxylin and eosin (H & E) (18). They recommended the use of tissue imprints with examination by the Wright-Giemsa stain and various cytochemical reactions. The University of Chicago study was based only on H & E stained sections and thus has confirmed the recommendations of the WHO study. If these recommendations had been followed, those cases the panel pathologists identified as ML-undifferentiated would have been correctly categorized as ML-histiocytic type and the rate of agreement would have increased from 74% to 84%. Seven percent of the cases in this category (ML-undifferentiated) were incorrectly termed ML-mixed (lymphocytic and histiocytic) type, an error which probably arose from an improper application of histologic criteria. Variations in nuclear size will be encountered even in lymph node sections in which the majority of the cells are of similar origin because some nuclei will be cut near the nuclear pole while others will be cut through the center of the nucleus or transversely. Thus, a cell population which contains nuclei of varying size does not justify the designation "ML-mixed." The criterion for this histologic diagnosis is a cell population made up of a mixture of large cells and smaller cells that have the morphologic appearance of the "poorly differentiated lymphocyte." It should be noted that only 2% of the cases in this category (ML-undifferentiated) were mistakenly considered to be poorly differentiated lymphocytic ML.

The level of agreement concerning ML-lymphocytic type varied from 64% in those composed of poorly differentiated lymphocytes to 72% in those designated as well-differentiated lymphocytic. The fact that the group of pathologists considered 9% of the cases in the former category to be ML-undifferentiated or -histiocytic may reflect our failure to appreciate a distinct morphologic and clinical entity recently described by Nathwani et al (19), ie, ML-lymphoblastic. Cases such as these were previously categorized in the Rappaport classification as ML-undifferentiated or -poorly differentiated lymphocytic primarily because of the relatively large nuclei in these cells. It has also been difficult to differen-

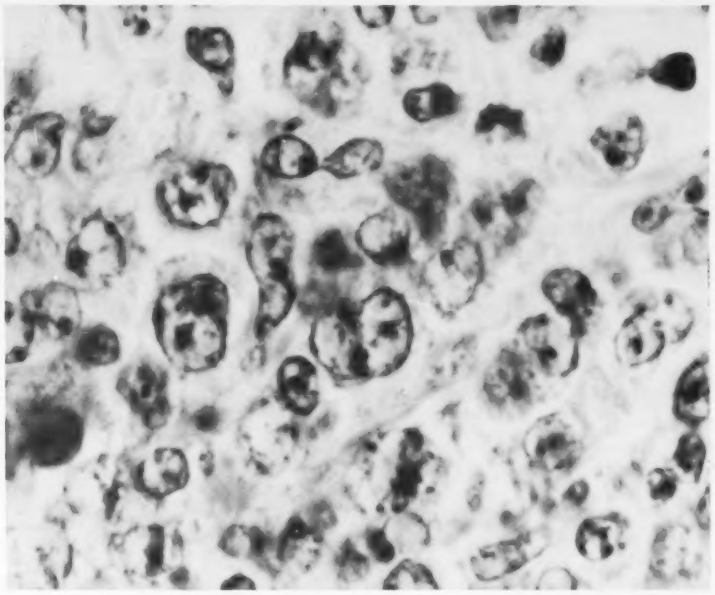

FIGURE 7.—Cytology of histiocytic lymphoma. Population of large cells with large round or slightly irregular nuclei. (H & E stain, × 1100.)

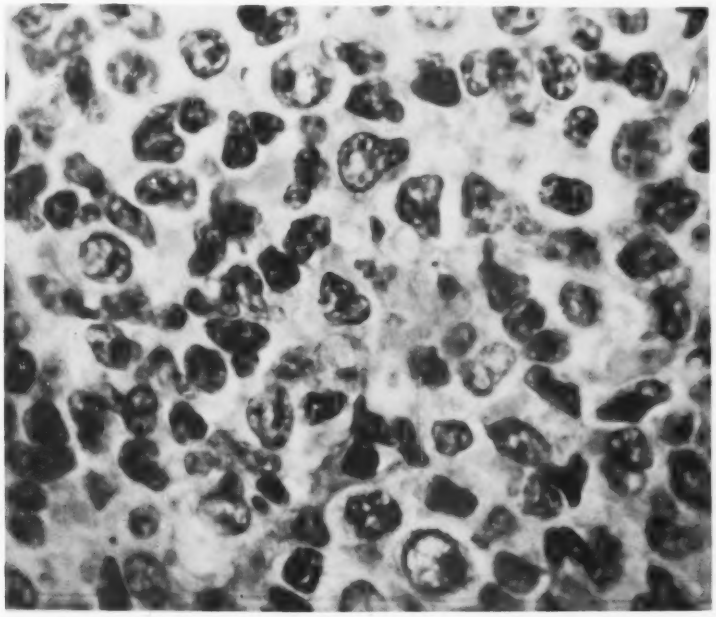

FIGURE 8.—Cytology of mixed (lymphocytic and histiocytic) lymphoma. Population of large and small cells with the latter having small, irregular, and indented nuclei. (H & E stain, × 1100.)

tiate some poorly differentiated lymphocytic tumors from well-differentiated lymphocytic lymphomas because the cytology in poorly differentiated lymphocytic ML varies from case to case; some lesions have a monotonous population of small cells with indented, irregular nuclei, while others have a mixture of small cells with irregular nuclei and small cells with more regular nuclei. Some workers have designated this group ML-intermediate lymphocytic, a term which has not been accepted widely because it does not provide a precise criterion that will permit good reproducibility.

The major area of disagreement in the Rappaport classification is in the category of ML-mixed (lymphocytic and histiocytic). Many have criticized this group because of the terminology, ie, lymphocytic and histiocytic, and recently immunologic data have demonstrated the large cells in this type of ML to be of B lymphocytic origin (9). Several of the newly proposed classification schemes, however, contain a diagnostic category which reflects a mixture of large and small cells (11,12). Thus, aside from the problem of terminology, the problem of diagnostic reproducibility remains whether we call these cells histiocytes and lymphocytes or simply large and small cells.

In the Chicago study the agreement in diagnoses in this category was only 69%. Twelve percent of the cases reported to be ML-mixed (lymphocytic and histiocytic) by the LPP were interpreted by the group of pathologists to be ML-poorly differentiated lymphocytic. This category presents the most difficult diagnostic problem because on the one hand it is frequently confused with reactive follicular hyperplasia and on the other its reproducibility in the cytologic subclassification of non-Hodgkin's lymphoma is poor. Clinical studies have shown the survival of patients with ML-mixed to be quite similar to that of patients with ML-poorly differentiated (1); thus, the critical distinction is between ML-mixed and ML-histiocytic. Difficulties in classification can be minimized by limiting the use of the term ML-mixed to those cases in which the cell population is composed of approximately 50% large and 50% small cells with irregular indented nuclei. Recent immunologic data have demonstrated that it is no longer appropriate to use the terms histiocytic and lymphocytic in identifying this category; this group should be referred to as ML-mixed. Because of the subjective aspects of this interpretation, however, good reproducibility will probably not be achieved with the techniques currently used in the diagnosis of non-Hodgkin's lymphomas.

From the results of the SWOG study the degree of agreement by the institutional pathologists with the LPP consultant was determined concerning the cytologic subclassification of the non-Hodgkin's lymphoma (16). Table 1 compares the agreement in the Chicago study with that of the SWOG study.

TABLE 1.—Reproducibility of cytologic classification of ML

ML	% reproducibility	
	Chicago study	SWOG study
Undifferentiated	58	—
Histiocytic	74	61
Mixed (lymphocytic and histiocytic)	69	50
Lymphocytic, poorly differentiated	64	49
Lymphocytic, well differentiated	72	55

THE RAPPAPORT CLASSIFICATION AND CHILDHOOD LYMPHOMA

Most studies concerned with the clinical significance of the Rappaport classification have dealt with ML in adults, and of the published studies of childhood lymphoma, only four have used the Rappaport classification (20–23). All of these studies have confirmed that nodular lymphomas are rare in childhood. Hence, nodularity, one of the most useful and histologically one of the most reproducible criteria of the Rappaport classification, cannot be applied in this age group. Table 2 shows the relative frequency of the various cytologic types in the diffuse lymphomas in childhood from four series. From these data it is apparent that the most common cytologic types of non-Hodgkin's lymphoma in childhood are ML-histiocytic, -undifferentiated, and -poorly differentiated lymphocytic. As with the diffuse lymphomas in adults (1), the overall survival of patients with these diffuse lymphomas has been poor irrespective of cell type (20).

I believe that the diffuse lymphomas of children must be re-evaluated in view of the recent studies of the so-called convoluted lymphocytic lymphoma. This disorder, which was originally described by Barcos and Lukes (24), appears to be a distinct clinicopathologic entity that affects primarily males (2:1) and often presents with a prominent mediastinal mass and early bone marrow involvement. Smith et al (25) have shown that one such case was of T-cell origin. The importance of this morphologic entity was rapidly recognized and this type of diffuse lymphoma was promptly added to several of the new classifications of non-Hodgkin's lymphoma.

Rappaport and associates recently described a series of patients with lymphoma, most of whom were < 20 years of age. They consider that these patients are similar to those described by Barcos

TABLE 2.—Cytologic distribution in non-Hodgkin's lymphomas in childhood

Diffuse lymphoma	Glatstein et al (ref 20)	Hutter et al (ref 22)	Murphy et al (ref 21)	Pinkel et al (ref 23)
Histiocytic	13	2	10	19
Poorly differentiated lymphocytic	11	16	5	—
Undifferentiated	4	4	9	45
Mixed	3	—	—	—
Unclassifiable			5	

and Lukes (24), but they have observed some variation in the cytology. Morphologically these tumors could be divided into those made up of neoplastic cells that contain convoluted nuclei and those made up of round, non-convoluted nuclei. Because their cytologic appearance was similar to that of lymphoblasts, Nathwani et al (19) applied the term ML-lymphoblastic to this neoplasm.

The clinical significance of the Rappaport classification in childhood lymphomas at this time appears to be uncertain. There is no doubt that the classification can be applied, but the variation in the types of non-Hodgkin's lymphoma in childhood, as indicated in the studies recorded in table 2, suggests that its previous application may have suffered from the poor reproducibility observed in the diffuse lymphoma category. The entity described by Barcos and Lukes (24) and the non-convoluted group observed by Nathwani et al (19) have most assuredly been included in these previous series as ML-histiocytic, -poorly differentiated lymphocytic, and -undifferentiated non-Burkitt. Presently, it is clear that with the exception of ML-well-differentiated lymphocytic, all diffuse lymphomas have a poor prognosis in both children and adults.

DISCUSSION

Clinical studies have shown that the Rappaport classification of non-Hodgkin's lymphomas does provide information that is clinically significant. Certain parameters of this classification, ie, the evaluation of the architectural arrangement of the neoplastic cells into a nodular or diffuse pattern, are highly reproducible morphologically. Other aspects of this classification, ie, the cytologic subclassification, have not in general reached a similar high level of reproducibility. The diagnostic categories of diffuse histiocytic and nodular poorly differentiated lymphocytic lymphoma have been shown in the SWOG study to be the most reliable

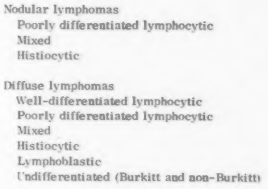

FIGURE 9.—Modified Rappaport classification of non-Hodgkin's lymphoma.

histologic diagnosis in this classification. The category of ML-mixed (lymphocytic and histiocytic) is the most problematic category and presents difficulties of reproducibility as well as differentiation from reactive follicular hyperplasia. The group identified as ML-undifferentiated is the least reliable diagnostic category unless the recommendations of the WHO study group are followed.

The Rappaport classification was proposed prior to the implementation of immunologic tests to determine more precisely the origin of the abnormal cells. That the classification is not biologically correct cannot be argued. Recent studies have provided information which makes it possible to modify this classification (fig 9) without altering its clinical usefulness. The term ML-mixed should be used to identify the category previously indicated as ML-mixed (histiocytic and lymphocytic) and the category of ML-lymphoblastic should be included in the classification of the diffuse lymphomas.

As pathologists, we should be striving for diagnostic reproducibility of clinically significant diagnostic categories. We may change the names applied to these categories in order to be noncommital on the one hand or more biologically correct on the other, but diagnostic reproducibility remains a problem that will not be improved by this tactic alone. The application of objective laboratory technology may in the future provide us with groups within the non-Hodgkin's lymphomas which are more biologically correct. It remains to be proven, however, whether they will be clinically useful.

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Pathology of the Non-Hodgkin's Lymphomas: New Classifications [1]

Ronald F. Dorfman [2,3,*]

SUMMARY

This paper briefly reviews the various classifications proposed as alternatives to that of Rappaport. Rappaport's classification is valuable because it is applicable to clinicopathologic studies, but there are areas of contention. Following the Airlie Conference, which failed to resolve the current controversy about classification, the National Cancer Institute proposed to support a retrospective study of 1000 cases of non-Hodgkin's lymphoma, during which the various classifications will be applied to the biopsy slides by a selected panel of pathologists. It is hoped that this study will meet the urgent need for a classification which will eliminate controversial terminology and will employ terms acceptable to pathologists in their daily diagnostic work and to hematologists and oncologists burdened with the choice of therapy for patients affected by the non-Hodgkin's lymphomas.

[Cancer Treat Rep 61:945–951, 1977]

The classification proposed by Rappaport et al (1) in 1956 and subsequently modified by Rappaport (2) in 1966 (fig 1) gained little attention or acceptance until the studies of Jones et al (3), with which I was involved, demonstrated that this classification was applicable to clinicopathologic investigations. Subsequent studies from the NCI (4,5) and from other institutions (6,7) confirmed these conclusions. This consensus enabled clinicians from many medical centers in the US and abroad to compare the results of various modes of radiation therapy and chemotherapy. Rappaport's classification was adopted by the Lymphoma Pathology Panel for Clinical Trial Studies (8) which serves cancer chemotherapy groups throughout the US and in a number of other countries.

Satisfaction with the results of collaborative clinicopathologic studies using Rappaport's classification was tempered by a rash of letters (9–12) and published reports (13–16) which questioned the validity of Rappaport's terminology and the concepts inherent in his classification. It has also become

Nodular	Diffuse
Lymphocytic, well-differentiated	
Lymphocytic, poorly differentiated	
Mixed cell (lymphocytic and histiocytic)	
Histiocytic	
Undifferentiated	

FIGURE 1.—Rappaport classification (1966).

apparent that 25 institutions in Great Britain involved in the British National Lymphoma Investigation have accepted as their working classification that of Bennett et al (10). A European consortium has proposed its own classification of the non-Hodgkin's lymphomas, now recognized as the "Kiel classification" (11,14), because it is based chiefly on concepts propounded by Lennert et al (14) from the University of Kiel, West Germany. In the US, Lukes and Collins (13) have proposed a new approach which relates the malignant lymphomas to the B- and T-lymphocytic systems and alterations in lymphocyte transformation.

In an attempt to resolve the controversy resulting from these new classifications, I presented a compromise "working classification" at the March 1974 meeting of the International Academy of Pathology in San Francisco (15). Notwithstanding the confusion resulting from this spate of classifications, Mathé et al (17) have introduced yet another system

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in their international histologic classification, a publication of the World Health Organization (WHO).

Before discussing and analyzing these new classifications, I shall briefly review recent observations which clearly indicate the need for changes in terminology. These are based on continuing morphologic studies, both light and electron microscopic (18), and the application of recently devised techniques for the identification of cell types by the demonstration of surface and intra-cytoplasmic immunoglobulins and/or specific membrane receptor sites (16,19).

The elegant studies of Jaffe et al (19), the results of which we have confirmed (15), have provided convincing evidence that the cells of nodular lymphomas derive from follicular B lymphocytes, thus substantiating the term "follicular lymphomas." Our ultrastructural studies (18) also support the contention that the nodular lymphomas have a close anatomic relationship to germinal centers. Immunologic and ultrastructural studies cast doubt on the concept of so-called mixed lymphomas of the lymphocytic and histiocytic type within the spectrum of the follicular lymphomas, and provide evidence that these lesions exhibit a range of morphologic variation from small lymphocytic cells, with characteristically indented and angulated nuclear membranes, to larger transformed lymphocytes, heretofore interpreted as histiocytes.

Objections have been raised to the use of the terms "well-differentiated" and "poorly differentiated" as applied to the lymphocyte. In vitro incubation of "mature" and "well-differentiated" lymphocytes with phytohemagglutinin and other mitogens has shown that these cells are capable of transformation into large "blastoid forms" (20,21). A similar phenomenon presumably occurs in vivo with the production of large lymphoid cells. The small lymphocyte may thus behave as a stem cell.

Some authors have hypothesized (13,14) and others have provided evidence, based on the detection of surface immunoglobulins and specific membrane markers (16), that some lymphomas hitherto classified as "histiocytic" are of lymphoid origin. The nature of Burkitt's tumor has always been the subject of some controversy. This neoplasm was classified as an undifferentiated lymphoma at the WHO meeting in 1967 (22); however, there is now convincing immunologic evidence indicating that Burkitt's lymphoma cells are of B-lymphocytic origin (16,23).

Time does not permit an in-depth analysis of each classification. I shall thus emphasize the conceptual and terminologic similarities inherent in these classifications in an endeavor to resolve some of the confusion. It is also appropriate to express my reservations and my objections to some of the newly proposed terms.

The Bennett, Farrer-Brown, and Henry Classification (Fig 2) (10)

The concepts underlying this classification certainly appear valid and the terminology is reproducible and easy to apply. Nonetheless, I have the following reservations. The classification of Bennett et al retains the terms "well and poorly differentiated." It fails to include the eponym "Burkitt's lymphoma" as a distinct entity, and has lumped within the poorly differentiated lymphocytic group, not only Burkitt's tumor, but the "mediastinal convoluted or T-cell lymphoma" of childhood and adolescence (24,25). As is well known, these lymphomas have recognizably different morphologic features and vastly different natural histories and responses to therapy.

The inclusion of extramedullary plasmacytoma in this classification, merely on the basis of origin from B lymphocytes, is questionable since the natural history and management of plasmacytoma and of multiple myeloma is so different from that of the non-Hodgkin's lymphomas. These pathologists, particularly Henry (26), are seemingly convinced that electron microscopic findings allow the specific identification of "true histiocytes," but many others are far from convinced that these parameters provide proof of the histiocytic origin of these cells.

There is now compelling evidence that mycosis fungoides represents a malignant lymphoma which arises primarily in the skin, and subsequently involves the lymph nodes, other components of the reticuloendothelial system, and viscera (27). In this disorder, and equally in Sézary's syndrome (28), the atypical lymphoid cells (mycosis cells) appear to be T cells. Thus, it is appropriate to include mycosis

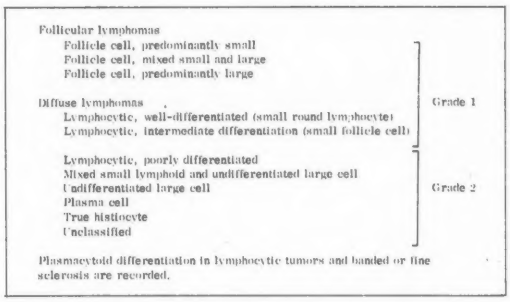

FIGURE 2.—Classification of non-Hodgkin's lymphomas (Bennett, Farrer-Brown, Henry, et al, 1973).

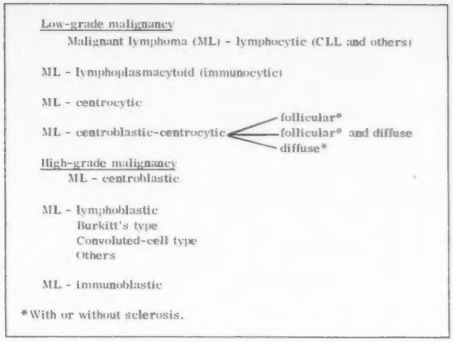

FIGURE 3.—Kiel classification of non-Hodgkin's lymphomas (Lennert, Kiel, Germany, 1974).

fungoides in any new classification of non-Hodgkin's lymphomas, which Bennett et al have failed to do.

The Kiel Classification (Fig 3) (11,14)

In their proposal for a standardized system of reporting human lymph node morphology in relation to immunologic function, Cottier et al (29) have recommended terms that are descriptive rather than those based on "as yet debatable functional interpretations." Thus, they use the term "large lymphoid cell" in preference to "immunoblast." The authors of the Kiel classification (11,14) have ignored this recommendation and have included terms such as "immunocytoma" and "immunoblastoma," derived from the concepts of Lennert et al (14) and of Lukes and Collins (13). Dameshek (30) proposed the term "immunoblast" for the cell he considered to be the forerunner of the immunocompetent plasmocytes and lymphocytes (active immunocytes). Lukes and Collins have introduced the term "immunoblastic sarcoma of B cells" to describe a lymphoma of presumed transformed B cells which develops in individuals with abnormal or defective immune states. This application of the term appears to be a departure from Dameshek's concept that the immunoblast is a precursor cell rather than a transformed lymphocyte.

According to Lennert et al (14), "reticulosarcomas" (histiocytic lymphomas) originate from B-cell-derived immunoblasts. In the Kiel classification, tumors formerly diagnosed as "histiocytic lymphoma" are reclassified as malignant lymphoma, immunoblastic, or centroblastic if they are considered to arise from follicular center cells. In their descriptions of the Kiel classification, Gerard-Marchant et al (11) and Lennert et al (14) have provided criteria which are confusing and conflicting and would be most difficult for the vast majority of pathologists to apply in their daily diagnostic work. They state initially that the diagnosis of centroblastic lymphoma is justified only when it is clearly established, either in part of the affected node or from a previous biopsy, that the neoplasm took its origin from the follicular center cell. They subsequently state that "generally speaking, these two types (immunoblastic lymphoma and centroblastic lymphoma) are clearly distinguishable." They excluded a histiocytic type of lymphoma from their classification, even though Lennert et al (14) subsequently wrote that "true reticulocytic or histiocytic lymphomas exist but are apparently rare."

The Kiel classification also seeks to impose upon pathologists entirely new terms, ie, "centrocytic" and "centroblastic," for lymphomas of follicular center cell origin. Lennert (31) had previously designated these lymphomas as "germinocytic" and "germinoblastic" respectively, but recognized that these terms would invite confusion with germinal cell tumors involving the gonads. Since follicular (nodular) lymphomas frequently involve the bone marrow (32) and not infrequently the peripheral blood ("lymphosarcoma cell" leukemia) (33), it appears that hematologists are being faced with the term "centrocytic-centroblastic leukemia"!

At a number of institutions in the US (3–5,15,32) and abroad (6), carefully controlled clinicopathologic studies using the Rappaport classification have clearly indicated the importance of identifying lymphomas with a follicular (nodular) pattern in terms of age, sex, and racial distribution (15); topographic distribution of lesions (32); and natural history and response to therapy (3). We have demonstrated that this applies equally to cases in which the follicular pattern is focal (34). However, we and other investigators have clearly shown that diffuse lymphomas, whether or not they are composed of cells cytologically identical to those observed in follicular lymphomas, are associated with a less favorable prognosis (3). Using the terminology of Lukes and Collins (fig 4), Butler et al (35) have confirmed our observations. They stated that "as far as survival is concerned the most important histological feature of a lymphoma is its pattern, whether diffuse or follicular." Gerard-Marchant et al and Lennert et al have not only ignored these observations but have stated quite dogmatically that the alteration in pattern does not necessarily affect the prognosis adversely and that the cytologic type is of greater import in this regard. However, they provide no clear evidence based on carefully controlled clinicopathologic studies to support their contention.

The Lukes and Collins Classification (Fig 4) (13)

In discussing this classification, I shall emphasize the difficulties that I and other pathologists have encountered in attempting to apply it to clinicopathologic evaluation. Lukes and Collins have made a major contribution by demonstrating the morphologic identification of the convoluted lymphocytic lymphoma and emphasizing its predilection for the mediastinum, its frequency in adolescent boys, and its propensity to involve the bone marrow, peripheral blood, and central nervous system (24). On the other hand, Nathwani et al (25) recently reported that mediastinal lymphomas with an identical clinical presentation may be composed of non-convoluted lymphoblasts, and proposed the term "malignant lymphoma, lymphoblastic" for this form of lymphoma.

Lukes and Collins have emphasized that lymphoma cells with cleaved nuclei originate in lymphoid follicles and that the pathologist can recognize follicular center-cell lymphomas even when a nodular pattern is not evident. Lukes also has implied that he agrees with Gerard-Marchant et al (11) and Lennert et al (14) that the prognosis of lymphomas of follicular center-cell origin is dependent on the identification of the specific cell type and not on the architectural pattern (nodular versus diffuse). This conclusion is apparently based on studies performed at the Royal Marsden Hospital, London, England.[1] However, the paper of Peckham et al (36), of which Lukes is a co-author, clearly demonstrates that nodular lymphomas show a more favorable 5-year survival than diffuse lymphomas.

While concepts based on a presumed functional capacity of the component cells deserve close study, we do not yet have sufficient information to clearly subdivide the malignant lymphomas into B- or T-cell types.

Lukes and Collins seem to have had the same difficulty as the authors of other new classifications in identifying a "true" histiocytic lymphoma and in distinguishing it from immunoblastic sarcoma of B- and T-cell types and from large cleaved and non-cleaved follicular center-cell lymphomas. It is clear that the vast majority of pathologists will have even more difficulty. Lukes and Collins have eliminated from their classification the category of mixed-cell lymphomas, in which small and large cells are evident without appreciable preponderance of each type, thus making it difficult for pathologists to recognize such lymphomas and to classify them properly.

The eponym Burkitt's lymphoma has now been universally accepted. Lukes and Collins have proposed that Burkitt's tumor is a "small non-cleaved follicular center cell" lymphoma even though in its preponderance in black African children, in its predilection for the bones of the jaw, orbit, and the gonads, and in its fulminating clinical course in untreated patients, this lymphoma does not bear the slightest resemblance to currently recognized follicular (nodular) lymphomas. I predict that attempted substitution of the term "small non-cleaved follicular center-cell lymphoma" for the eponym Burkitt's lymphoma will meet with considerable resistance from clinicians, if not from pathologists. Indeed, the greatest barrier to the acceptance of the Lukes and Collins classification is its cumbersome terminology.

I. U-cell (undefined) type

II. T-cell types
1) Mycosis fungoides and Sézary's syndrome
2) Convoluted lymphocyte
3) ? Immunoblastic sarcoma (of T cells)
4) ? Hodgkin's disease

III. B-cell types
1) Small lymphocyte (CLL)
2) Plasmacytoid lymphocyte
3) Follicular center-cell types (follicular, diffuse, follicular and diffuse, and sclerotic)
a) small cleaved
b) large cleaved
c) small non-cleaved
d) large non-cleaved
4) Immunoblastic sarcoma (of B cells)

IV. Histiocytic type

V. Unclassifiable

FIGURE 4.—Lukes and Collins classification.

The International Histological (WHO) Classification (Mathé et al) (17) (Fig 5)

While incorporating some of the new terms such as "immunoblastic" and retaining established terms such as "Burkitt's tumor," this classification becomes retrogressive when it employs the term "lymphosarcoma." On previous occasions (15,37,38) I have echoed the comments first made by Jackson and Parker (39) many years ago concerning the confusion engendered by this designation. To some, lymphosarcoma is synonymous with malignant lymphoma; to others it implies a lymphocytic lymphoma. Indeed, it was not too long ago that I encountered a pathology report which offered the diagnosis "lymphosarcoma of reticulum cell type"!

The term "prolymphocytic" in the WHO classification makes use of a designation familiar to hematologists from their examinations of Romanovsky-stained preparations, but not to pathologists work-

[1] Lukes RJ. Personal communication.

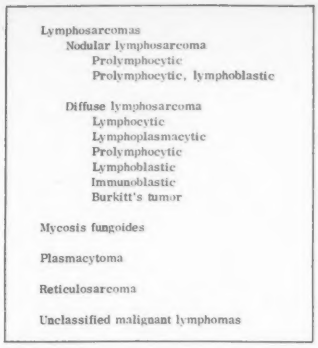

FIGURE 5.—WHO classification of malignant lymphomas (Mathé, Rappaport, O'Conor, et al, 1976).

ing with histologic sections stained with hematoxylin and eosin. Furthermore, Galton et al (40) have recently identified a new entity, prolymphocytic leukemia, which differs from the leukemic phase of the nodular (follicular) lymphoma of lymphocytic type (33).

The WHO classification defines reticulosarcoma as a malignant tumor composed of large cells of uncertain origin which show evidence of the production of argyrophilic fibrils or phagocytosis or both. It has become increasingly evident that sclerosis may also be associated with lymphomas which, on the basis of both architecture and cytology, are clearly follicular (nodular) as described by Bennett (41) and that these are of B-cell origin (19). Rosas-Uribe and Rappaport (42) have also described a trabecular form of sclerosis, and although the lymphomas in their series were of large cell type, their origin from histiocytes was as conjectural as that of the "histiocytic" lymphomas described above. Thus, it is debatable whether the presence of argyrophilic fibers, even though these surround individual cells, proves that these cells are of histiocytic (reticulum cell) origin.

The WHO monograph is well illustrated and, notwithstanding these criticisms, I believe it will make an important contribution to our understanding of the malignant lymphomas.

The Dorfman Classification (Fig 6) (9,15)

In accordance with the commendable recommendations of Cottier and co-workers (29), this classification employs descriptive terminology and does not impose contentious and cumbersome designations upon practicing pathologists, hematologists, and oncologists. It relies on data from the most

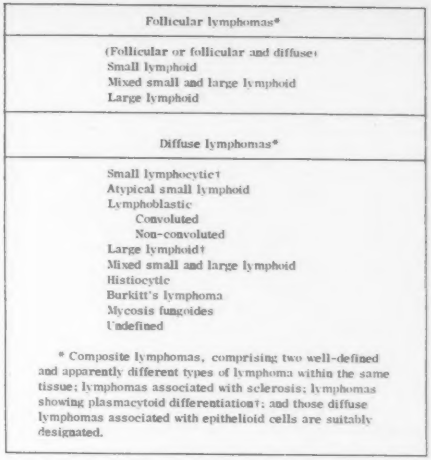
Follicular lymphomas*
(Follicular or follicular and diffuse†
Small lymphoid
Mixed small and large lymphoid
Large lymphoid
Diffuse lymphomas*
Small lymphocytic†
Atypical small lymphoid
Lymphoblastic
Convoluted
Non-convoluted
Large lymphoid†
Mixed small and large lymphoid
Histiocytic
Burkitt's lymphoma
Mycosis fungoides
Undefined
* Composite lymphomas, comprising two well-defined and apparently different types of lymphoma within the same tissue; lymphomas associated with sclerosis; lymphomas showing plasmacytoid differentiation†; and those diffuse lymphomas associated with epithelioid cells are suitably designated.

FIGURE 6.—Working classification of non-Hodgkin's lymphomas (Dorfman, 1974; modified, 1976).

recent ultrastructural and immunofluorescence studies and from techniques used to detect membrane receptor sites. It emphasizes the imperative need to identify lymphomas with a follicular pattern because of their favorable prognosis (despite their tendency for early widespread dissemination) and their distinctive racial distribution, sex incidence, and age incidence. Despite allegations to the contrary (11), "a fundamental division between low grade and high grade malignant lymphomas *is* implicit in the terminology." The low-grade lesions comprise the group of follicular lymphomas and, in the diffuse category, the small lymphocytic lymphoma, which corresponds to Rappaport's well-differentiated lymphocytic type. Like the majority of the newly proposed schemes, this classification retains the term "histiocytic" despite its controversial implications, albeit recognizing that the criteria proposed for distinguishing between a large lymphoid and histiocytic lymphoma may ultimately prove to be erroneous. The recent observations of Nathwani et al (25) have made it evident that not all of the mediastinal lymphomas affecting adolescent boys are composed of convoluted lymphocytic cells. Thus, this classification includes the term "lymphoblastic, convoluted and non-convoluted."

None of the new classifications has paid specific attention to childhood lymphomas even though they require a separate classification (fig 7) because virtually all have a diffuse pattern. Nodular (follicular) lymphomas of all types are exceptionally rare in children and adolescents, and I have yet to encounter a diffuse "well-differentiated" lymphocytic lymphoma in a child.

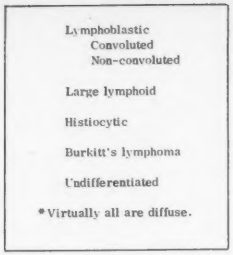

FIGURE 7.—Classification of childhood lymphomas* (Dorfman, 1976).

DISCUSSION

The number of classifications of non-Hodgkin's lymphomas recently proposed as alternatives to that of Rappaport has dismayed clinicians faced with the choice of therapy and statisticians who attempt comparative studies. As a result, Dr. Vincent DeVita, Director of the Division of Cancer Treatment, NCI, invited me to convene a conference of pathologists and clinicians in an effort to resolve the current controversy. This meeting, which was co-chaired by Dr. Costan Berard, Head of the Hematopathology Section, Laboratory of Pathology, NCI, took place at Airlie House, Warrenton, Va, on September 4 and 5, 1975. The Airlie Conference failed to produce any form of compromise, but it enabled clinicians to air their concerns and voice their objections to the pathologists responsible for the newly suggested classifications. The clinicians urged an early resolution of the current confusion and called for a universally acceptable classification to replace that of Rappaport.

The NCI then offered to support a large-scale retrospective review of patients with non-Hodgkin's lymphomas which would assess the relative clinicopathologic value of the various histopathologic subclassifications. This project will entail a histopathologic review of the diagnostic biopsy material from 1000 patients with non-Hodgkin's lymphomas. A number of institutions have been selected to participate in this study based on their access to case material which will satisfy the entry and staging requirements. Each institution selected will obtain the clinical data in a format suitable for later coding and computerization at a selected central facility.

A panel of pathologists designated by the NCI will visit each contributing institution and will subclassify each of the cases according to one or more of the suggested systems. The pathologists will submit their diagnoses for all cases to the central facility, and the clinical and histopathologic data will then receive a detailed analysis. It is hoped that this carefully controlled clinicopathologic study will indicate which of the newly proposed classifications is most adaptable to comparative clinical trials and is most easily utilized by practicing pathologists.

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Functional Markers: A New Perspective on Malignant Lymphomas[1]

Elaine S. Jaffe,* Raul C. Braylan, Koji Nanba, Michael M. Frank, and Costan W. Berard[2,3]

SUMMARY

The study of malignant lymphomas for membrane surface markers and enzyme histochemical features often permits the identification of the cytogeneology of the neoplastic cells. Furthermore, the application of these techniques to frozen tissue sections allows the interrelationships of various cell types present, both benign and malignant, to be observed. Recent studies reviewed in this paper indicate that most large cell malignant lymphomas (so-called histiocytic) are of lymphocytic origin, usually of the B-cell type (11 of 17 cases). Rare tumors composed of neoplastic T cells (one of 17 cases) or true histiocytes (one of 17 cases) occur. In four of 17 cases no markers were demonstrable. Lymphoblastic lymphomas exhibit some heterogeneity of their membrane surface markers, forming both EAC (five of nine cases) and E (five of nine cases) rosettes. However, the invariable presence of terminal deoxynucleotidyl transferase activity links these tumors to thymic or T-cell lymphoblasts. Acid-phosphatase and β-glucuronidase activities are also consistent cytochemical markers for these tumors. Studies of diffuse lymphocytic lymphomas of intermediate differentiation indicate that these B-cell tumors have immunologic features intermediate between follicular lymphomas and well-differentiated lymphocytic malignancies. Cytochemically and immunologically they appear related to follicular cuff lymphocytes. Studies of 49 cases of nodular lymphoma confirm the follicular B-cell nature of the neoplastic cells. Additional studies on the localization of T lymphocytes within these tumors indicate that morphologically normal T cells are also present within the nodules in most cases. These observations suggest that the T lymphocytes, although benign, may be functionally interacting with the neoplastic B cells.

[Cancer Treat Rep 61:953–962, 1977]

Malignant lymphomas have traditionally been classified morphologically, and the classification of Rappaport published in 1966 (1), with minor modifications (2), has been the most widely used for clinicopathologic studies (fig 1). However, the recognition of malignant lymphomas as neoplastic disorders of the immune system has made possible a new functional approach to the classification and understanding of these tumors. Immunologic knowledge and techniques have been brought to bear on clinical and pathologic problems; for example, the

Nodular
- Lymphocytic, poorly differentiated
- Mixed lymphocytic-histiocytic
- Histiocytic

Diffuse
- Lymphocytic, well-differentiated
- Lymphocytic, intermediate differentiation
- Lymphocytic, poorly differentiated
- Mixed lymphocytic-histiocytic
- Histiocytic
- Undifferentiated (Burkitt's type)
- Undifferentiated, pleomorphic (non-Burkitt)

FIGURE 1.—Classification of non-Hodgkin's lymphomas (1,2).

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Well-differentiated lymphocytic malignancies Chronic lymphocytic leukemia Well-differentiated lymphocytic lymphoma Waldenström's macroglobulinemia	B lymphocytic
Nodular (follicular) lymphoma Lymphosarcoma Lymphosarcoma cell leukemia	B lymphocytic
Burkitt's lymphoma	B lymphocytic
Mycosis fungoides Sézary's syndrome	T lymphocytic
Lymphoblastic lymphoma of childhood Acute lymphocytic leukemia (25%)	T lymphocytic
Histiocytic lymphomas	Variable
Malignant histiocytosis	Histiocytic

FIGURE 2.—Summary of cell surface markers in lymphoreticular malignancies.

concepts of "homing" and "traffic" of normal lymphocytes help to explain patterns of spread in these tumors. Likewise, the immunologic deficits manifested by these patients reflect the component of the immune system affected by the neoplasm.

The study of the neoplastic cells for the presence of cell surface markers and by functional assays typifies this approach. By analogy to normal cells, many of the tumors have been classified according to their presumptive cells of origin: T lymphocyte, B lymphocyte, or monocyte-macrophage (fig 2). Most non-Hodgkin's lymphomas appear to be of B-lymphocytic type. Moreover, subtle variations in surface markers permit us to assign some lymphomas to particular subpopulations; for example, both nodular lymphoma (3) and Burkitt's lymphoma (4) appear to be malignancies of follicular B cells, whereas well-differentiated lymphoid neoplasms are more closely related to medullary cord B cells (5). T-cell tumors are less common and include mycosis fungoides and the related entity, Sézary's syndrome (6,7). Lymphoblastic lymphoma (8–10) and acute lymphocytic leukemia (11,12) are also of T-cell origin. Subpopulations of T cells are as yet poorly understood, but there is evidence that, in some cases, Sézary cells may function as helper T cells (13). Alternatively, the identification of terminal deoxynucleotidyl transferase (Tdt) activity in the lymphoblastic tumors indicates that they may be related to thymic stem cells or T blasts (14).[4] True Histiocytic lymphomas (monocyte-macrophage series) are extremely rare, but histiocytic medullary reticulosis is one systemic neoplasm of proven histiocytic origin (15).

The lymphomas summarized above have been the subject of numerous reports and need not be discussed further. In this review, the emphasis is on several areas in which new data are available, namely, large cell ("histiocytic") malignant lymphomas, lymphoblastic lymphomas, and diffuse lymphocytic lymphomas of intermediate differentiation, and on recent studies of nodular lymphomas, particularly the T lymphocytes in these tumors.

Diffuse "histiocytic" lymphomas have been the subject of relatively few detailed functional studies (16,17). We recently completed a study of the membrane surface markers and histochemical profile of the neoplastic cells from 17 patients with large cell malignant lymphomas. Morphologically 13 of these tumors were classified as diffuse "histiocytic" and four were designated as undifferentiated, pleomorphic (2). The neoplastic cells were studied in suspension for spontaneous rosette (E) formation with sheep red blood cells (SRBC), receptors for complement (EAC), receptors for cytophilic antibody (IgGEA), and surface immunoglobulins (SIg) (4). The study employed enzyme histochemical techniques on frozen sections and cytochemical reactions on cytocentrifuge preparations from some cases to identify the following hydrolytic enzymes: acid phosphatase (AP) with and without tartrate, alkaline phosphatase (ALP), β-glucuronidase (BG), and a variety of esterases (EST) including α-naphthyl acetate esterase (A-EST), α-naphthyl butyrate esterase (B-EST), naphthol ASD chloroacetate esterase (ASDCl), and naphthyl ASD acetate esterase (NASDA) with and without NaF inhibition (4,18). Tables 1 and 2 respectively summarize the data regarding the immunologic and histochemical features of these 17 cases.

B-lymphocyte markers were identified in 11 of the 17 tumors. However, marked variation was encountered in the number of markers detected and in the percentages of neoplastic cells expressing particular markers. SIg, the most consistent marker, was present in all suitably evaluated cases. In seven of the 11 cases studied for individual heavy and light chains, IgM and κ were identified. Surface-bound IgM has also been the most frequent heavy chain class in other B-lymphocytic malignancies, including nodular lymphoma (19,20), chronic lymphocytic leukemia (CLL) (21), and Burkitt's lymphoma (4,22). This finding is not unexpected since IgM is the predominant immunoglobulin on normal peripheral blood B lymphocytes (23). In one case, only κ light chains were identified; heavy chains were not detected. However, this patient was not studied for IgD. None of the lymphocytes in these 11 cases contained significant hydrolytic enzyme activity.

Six of the 11 B-cell lymphomas developed in patients with a previous diagnosis of nodular lymphoma and these invariably manifested B-cell markers. Such tumors apparently result from a dediffer-

[4] Donlon JA, and Jaffe ES. Terminal deoxynucleotidyl transferase activity in malignant lymphomas. Submitted for publication.

TABLE 1.—Membrane surface markers of 17 large cell malignant lymphomas

Patient No.	Histology	Source	SIg	Clonality	EAC	IgGEA	E	B-EST	Markers identified*
47	Diffuse histiocytic	Lymph node	Not determined	—	21	17	28	0	—
91	Undifferentiated, pleomorphic	Colon	Not determined	—	16	0	3	0	—
210	Diffuse histiocytic	Peripheral blood	10	—	12	17	13	0	—
349	Undifferentiated, pleomorphic	Ascites	5	—	9	9	1	0	—
134	Diffuse histiocytic	Spleen	50	—	50	8	47	0	SIg, EAC
186	Diffuse histiocytic	Bone marrow	95	Mκ	7	93	10	0	SIg, EA
293	Undifferentiated, pleomorphic	Lymph node	62	κ	32	10	20	0	SIg, EAC
296	Diffuse histiocytic	Bowel	63	Mκ	38	0	20	0	SIg, EAC
323	Diffuse histiocytic	Lymph node	98	Mκ	29	19	2	0	SIg, EAC
171†	Diffuse histiocytic	Lymph node	75	—	14	19	5	0	SIg, (EAC), (EA)
180†	Diffuse histiocytic	Lymph node	92	—	43	12	11	0	SIg, EAC
181†	Diffuse histiocytic	Lymph node	Not satisfactory	—	50	Not determined	Not satisfactory	0	EAC
196†	Undifferentiated, pleomorphic	Lymph node	40	—	80	Not determined	6	0	SIg, EAC
251†	Diffuse histiocytic	Spleen	41	Mκ	39	50	59	0	SIg, EAC, EA
	Diffuse histiocytic	Lymph node	45	Mκ	64	41	55	0	SIg, EAC, EA
271†	Diffuse histiocytic	Peripheral blood	85	Mκ	17	21	2‡	0	SIg, (EAC), (EA)
174	Diffuse histiocytic	Lymph node	15	—	Not satisfactory	Not satisfactory	85	±	E
298	Diffuse histiocytic	Bone	0	—	33	19	2	+	(EAC), (EA), B-EST

*Parentheses = marker present on < 25% neoplastic cells.
†Previous diagnosis of nodular lymphoma.
‡Figure obtained after pretreatment with anti-human Ig.

TABLE 2.—Enzyme histochemistry of 17 large cell malignant lymphomas

Immunotype*	Patient No.	Histology	Source	Reaction of neoplastic cells									
				AP	T-AP	ALP	A-EST	B-EST	BG	ASDCl	NASDA	NaF NASDA	No.†
"Null" cell tumors	47	Diffuse histiocytic	Lymph node	–	–	–	–	–	ND‡	–	–	–	++
	91	Undifferentiated, pleomorphic	Colon	–	–	–	–	–	ND	–	–	–	+
	210	Diffuse histiocytic	Peripheral blood	++	–	–	++	–	ND	ND	ND	ND	–
	349	Undifferentiated, pleomorphic	Ascites	+	–	–	+	–	+	–	ND	ND	++
B-cell tumors	134	Diffuse histiocytic	Spleen	–	–	–	–	–	ND	–	–	–	+++
	186	Diffuse histiocytic	Lymph node	±	–	–	±	±	ND	–	–	–	+++
	293	Undifferentiated, pleomorphic	Lymph node	–	–	–	–	–	–	–	+	–	++
	296	Diffuse histiocytic	Bowel	+	–	–	±	–	±	–	–	–	++
	323	Diffuse histiocytic	Lymph node	–	–	–	–	–	–	ND	–	–	++
	171	Diffuse histiocytic	Lymph node	–	–	–	–	–	ND	–	–	–	++
	180	Diffuse histiocytic	Lymph node	–	–	–	–	–	ND	–	–	–	++
	181	Diffuse histiocytic	Lymph node	–	–	–	–	–	ND	–	–	–	+
	196	Undifferentiated, pleomorphic	Lymph node	–	–	–	–	–	ND	–	–	–	++
	251	Diffuse histiocytic	Spleen	–	–	–	–	–	–	–	–	–	++
		Diffuse histiocytic	Lymph node	–	–	–	–	–	–	–	–	–	++
	271	Diffuse histiocytic	Peripheral blood	–	–	–	–	–	++	ND	ND	ND	–
T-cell tumors	174	Diffuse histiocytic	Lymph node	++§	–	–	++§	++§	ND	–	–	–	+++
True histiocytic	298	Diffuse histiocytic	Bone	++	–	±	++	+	++	–	++	++	++

*See table 1.
†Macrophages.
‡ND = not determined.
§Reaction cannot be definitely localized to neoplastic cells.

entiation or overgrowth of the proliferative element of the neoplasm. A similar phenomenon occurs in blastic transformation of chronic myelogenous leukemia, in which the blasts retain the Ph[1] chromosome. Identical observations have been reported with other lymphoid neoplasms, ie, blastic transformation of CLL (24), and in Richter's syndrome, large cell malignant lymphomas supervening on CLL (17). In rare instances in which both the antecedent well-differentiated proliferation and the blastic tumor were studied, the membrane-bound immunoglobulins were of the same light and heavy chain class; this finding supports the concept that both tumors belong to one neoplastic clone.

One of these six cases with previous nodular lymphoma (patient 271) was distinctly unusual. Like the others, this tumor had B-cell features, including monoclonal SIg (IgMk) and rosette formation with EAC and IgGEA. No rosettes were formed with the control reagent, IgMEA. Surprisingly, the neoplastic cells also formed E rosettes. Additional studies indicated that the E-rosette formation was probably due to a cold-reacting antibody against SRBC on the surface of the neoplastic cells. E-rosette formation by the neoplastic cells was totally inhibited by pretreatment with anti-human Ig. Pseudo-rosette formation of this type has been reported in CLL (25).

Of the six tumors without B-cell markers, one (patient 174) had features suggestive of a T-cell lymphoma. The cells formed E rosettes and lacked detectable SIg. They could not be investigated for specific binding of EAC and IgGEA since they formed rosettes with SRBC at both 37°C and 4°C. E rosettes were thus formed with EAC, IgGEA, and the control reagent IgMEA. The tumor had numerous macrophages that exhibited diffuse cytoplasmic hydrolytic enzyme activity, but the neoplastic cells were apparently devoid of any such activity. This lymphoma was similar to three T-cell lymphomas we reported earlier (15), which also had abundant morphologically benign histiocytes. The accumulation of macrophages within these tumors might be accounted for by postulating the production of macrophage migration inhibition factor by the neoplastic cells. The neoplastic cells in these three tumors (15) were predominantly lymphoid with smaller numbers of large atypical "histiocytic" cells. Large-cell lymphomas of T-cell type may represent one end of a spectrum (analogous to that seen in nodular lymphomas) in which varying proportions of large "histiocytic" cells are seen with the smaller neoplastic lymphoid cells.

The neoplastic cells in one of the 17 tumors, occurring in a 14-year-old boy (patient 298), had markers consistent with a true histiocytic origin. They lacked SIg but formed rosettes with both EAC and IgGEA. In addition, they phagocytosed bound erythrocytes, a phenomenon we have seen only with cells of the monocyte-macrophage series. These cells also contained abundant hydrolytic enzymes, manifested as diffuse cytoplasmic positivity for AP, A-EST, BG, and NASDA, and weak staining for B-EST. Unlike the other cases, this tumor was primary in the bone (clavicle). The cells were large and pleomorphic, with abundant acidophilic cytoplasm, and the nuclei were large and often lobulated, with prominent eosinophilic nucleoli.

No immunologic markers were detected in the remaining four cases although only two were completely studied. The neoplastic cells in these two contained AP and A-EST, one of which also had BG. The staining pattern was not diffuse, as in cells of the monocyte-macrophage series; rather, the activity was present as discrete punctate dots, in one case restricted to the Golgi zone. This pattern of enzyme activity is seen in lymphocytes, both normal and neoplastic. It has been reported in T-cell tumors, but T-cell markers were not demonstrable in these cases. One tumor (patient 349) also lacked Tdt activity. One tumor (patient 210) had plasmacytoid features both morphologically and ultrastructurally (26). Mature plasma cells and myeloma cells are reported to contain AP activity. Unlike normal or neoplastic plasma cells, however, the neoplastic cells lacked detectable intracytoplasmic immunoglobulin.

This series is too small to permit any comment concerning clinical differences among large cell tumors of different cytogeneologies. Two of the four tumors without surface markers were classified as undifferentiated pleomorphic (non-Burkitt) and, in the future, it may be shown that these morphologically primitive tumors lack detectable membrane surface markers more often than do other types. We must study many more cases before it can be determined if tumors of a particular immunotype are consistently associated with either clinical or pathologic features.

The studies described above indicate the importance of histochemical and cytochemical techniques in the investigation of tumors postulated to be of histiocytic origin. Cytochemistry has been equally useful in the study of lymphoid malignancies. Recently, AP and BG have been demonstrated in a large number of T-cell tumors, particularly Sézary's syndrome (27), T-cell CLL (28), acute lymphocytic leukemia of T-cell type (29), and lymphoblastic lymphoma (LBL) (30).

Earlier we described surface markers of LBL (10) and now these studies have been expanded to include cytochemical techniques. Table 3 summa-

TABLE 3.—Membrane surface markers and cytochemical findings in 9 lymphoblastic lymphomas

Patient No.	Patient age/ sex	Mediastinal mass	Source	E*	EAC	IgGEA	SIg	AP†	BG	Tdt
87	12/F	+	Peripheral blood	7	85+	3	8	ND‡	ND	ND
157	23/M	+	Peripheral blood	10	9	4	8	ND	ND	ND
166	22/M	+	Peripheral blood	80+	70+	8	0	ND	ND	ND
162	18/M	+	Bone marrow	3	4	1	0	ND	ND	ND
240	19/M	+	Lymph node	7	30+	1	0	50§	80§	+
312	18/M	+	Pleural fluid	32+	34+	1	1	55§	18§	+
344	30/F	+	Pleural fluid	23+	16+	1	0	100¶	99¶	+
376	23/M	+	Pleural fluid	63+	Negative for receptors	Negative for receptors	0	94¶	99¶	+
306	60/M	–	Skin	20+	9	0	0	ND	63§	±
		–	Peripheral blood	6	3	2	ND	62§	18§	–

*Results are expressed as % of positive cells; + = marker identified on neoplastic cells.
†% of neoplastic cells positive for enzymes AP or BG.
‡ND = not determined.
§Multigranular reaction product.
¶Punctate perinuclear reaction product.

rizes the features of nine cases of LBL. Five were both studied cytochemically and assayed for Tdt activity.[5] AP and BG were found in all cases studied, regardless of the surface markers present. However, there was some variation in the percentages of positive cells and in the patterns of staining. The neoplastic cells from the two tumors had localized punctate activity in the perinuclear zone while in three others the cells exhibited multiple dot-like reactions. Of five tumors assayed for Tdt, four were unequivocally positive and one had borderline levels of this enzyme.[5]

We have previously reported on the presence of complement receptors in LBL (10). In this expanded study we found such receptors in five of nine cases. The recent identification of such receptors on fetal thymocytes (31) makes this finding easier to explain and further supports the thymic origin of these tumors.

The findings in a 60-year-old man (patient 306) (table 3) were atypical on both clinical and pathologic grounds. This LBL was primary in the skin. The cells formed E rosettes, but had only very weak activity for AP and BG and borderline levels of Tdt.[5] The patient's disease was restricted to the skin for 2 years and he never developed a mediastinal mass. Later he had involvement of the cerebrospinal fluid and peripheral blood (wbc count 80,000/mm^3). Both leukemic progression and meningeal involvement are features of LBL.

Nodular (follicular) lymphomas are a major subgroup of non-Hodgkin's lymphomas, and account for approximately 50% of all adult cases. Previously, we described surface membrane markers in nodular lymphomas and showed that normal follicular B lymphocytes (3) and the neoplastic cells both had avid complement receptors. Other investigators have found easily detectable SIg, usually of the IgM class with or without IgD (19,20). Our studies, which now include 49 specimens from 36 patients, have confirmed earlier observations. Strong binding of EAC, both in suspensions and on frozen sections, was seen in 48 of the 49 specimens. Thirty-one of 32 specimens studied for SIg showed bright staining of the neoplastic cells. Fifteen were evaluated for individual light and heavy chains, ie, κ and λ, as well as IgM, IgG, and IgA. In all instances the SIg was monoclonal with only a single light chain. IgM was the heavy chain in 13 of the 15 specimens. Only κ light chains were found in two, but these specimens were not studied for IgD. Two of five specimens studied for IgD were positive and in one of these both IgD and IgM were identified with only κ light chains. The coexistence of surface-bound IgD and IgM which has been reported in other B-lymphocytic tumors, most commonly in CLL, does not contradict the monoclonality of these neoplasms (32). Tests with an anti-idiotypic antibody showed that the IgD and IgM were of the same idiotype and even shared the same antibody specificity.

The percentages of T cells (E-rosette-forming cells [ERFC]) in lymph nodes involved by nodular lymphoma are somewhat variable but often higher than might be expected. In our series, lymph nodes from untreated patients contained a mean of 42% ± 12% ERFC. In recurrences after therapy the mean % of ERFC was somewhat lower (34% ± 18%). At present we have no evidence that these T cells are part of the neoplastic process, since cytologically they are invariably normal. After earlier studies we had speculated that the T cells probably

[5] *See* footnote 4.

were located in the internodular stroma, because these areas were populated by predominantly normal-appearing lymphocytes. Furthermore, with progressive replacement of the nodal parenchyma by tumor, the % of ERFC was reduced (3). However, the lack of a method for identifying T cells in sections precluded their precise localization.

We subsequently applied to nodular lymphomas the method of Tønder et al (33) for the identification of ERFC in frozen tissue sections, with slight modification. SRBC were pretreated with neuraminidase (E_N) as previously described (34). The frozen sections were incubated for 18 hours at 4°C with a solution of 0.5% E_N in 20% heat-inactivated fetal calf serum previously absorbed with SRBC. After incubation the sections were inverted for 30 minutes at 4°C and read without fixation. The sections were examined in parallel with serial frozen sections stained with hematoxylin and eosin. We studied 23 lymph nodes involved by nodular lymphoma, either the poorly differentiated lymphocytic (NPDL) or the mixed cell type. Eleven nodes were obtained before any therapy and 12 lymph nodes represented post-therapy recurrences. Seven spleens involved by NPDL were studied, three before therapy and four after therapy. Control tissues included normal or reactive lymph nodes and spleens, normal thymus, and lymph nodes involved by CLL of B-cell type, which contained negligible numbers of T cells.

The tissues studied by the frozen-section technique were also studied in suspension and the % of T cells was determined. The mean % of ERFC was 41% ± 13% in nodes obtained before therapy and 34% ± 19% in the recurrences. In the spleens the mean % of ERFC was 42% ± 9% before therapy and 27% ± 12% after therapy.

In lymph nodes involved by nodular lymphoma the strongest reactions with E_N were not internodular, as had been anticipated, but were intranodular, particularly at the periphery of the nodules. In a majority of cases, these perinodular reactions were particularly striking and assumed the configuration of the nodules with the densest adherence of E_N at the periphery and weaker reaction in the central portions. This localization was present in lymph nodes whether obtained before or after therapy. Of 11 lymph nodes obtained before therapy, eight showed a nodular or perinodular reaction that was equal to or greater than the internodular reaction. Only three cases showed a negative nodular reaction; in these the predominant E_N adherence was internodular. The nodular or perinodular reactions generally were less striking in the recurrences, but still were evident in seven of 12 cases. In five cases the predominant reactions were internodular and the nodules themselves were negative.

The findings were somewhat different in spleens involved by nodular lymphoma. Those areas of the malpighian follicles which were replaced by neoplastic cells showed only weakly positive reactions. The strongest reactions were at the periphery of the white pulp, an area thought to be populated normally by T cells (35). However, the peripheral T-cell reactions in spleens involved by nodular lymphoma were much greater than those in any of the normal spleens studied. These reactions did seem to correlate histologically with a prominent zone of normal lymphocytes and immunoblasts. The one case which did not show this peripheral white-pulp reaction also lacked the hyperplastic features described above.

The strong binding of E_N to the nodules in nodular lymphoma was unexpected, and we wanted to confirm that this adherence was due to the interaction of SRBC and T lymphocytes. The results of control studies appear to support this conclusion. Very strong reactions were observed between thymocytes in sections and E_N. In contrast, tissues involved by CLL, which contained few ERFC in suspension, showed essentially no binding to frozen sections and only rare isolated rosettes. Additional controls were performed on tissues involved by nodular lymphoma. The reaction was inhibited by trypsinization of the SRBC, a procedure known to inhibit the E-rosette phenomenon (35). We speculated that the SIg associated with the nodular lymphoma cells might have mediated the E binding via antibody activity, but pretreatment of frozen sections with anti-human immunoglobulin did not inhibit the reaction. Furthermore, the one case that was SIg-negative also exhibited a strong reaction. Similar incubations were performed using human and rabbit red blood cells because it has been reported that human and rhesus monkey (but not rabbit) red blood cells interact with human T lymphocytes in a manner similar to SRBC (36–39). With human red blood cells there was a weak but similar reaction to that observed with SRBC; however, the rabbit red blood cells did not demonstrate specific patterns of localization.

All of the above evidence indicates that the nodules of nodular lymphoma contain T lymphocytes. The significance of this finding is not as yet clear although these cells may well be reactive and not part of the neoplastic clone. On cytocentrifuge preparations, as mentioned above, these ERFC always appear cytologically normal. Furthermore, in patients with earlier nodular lymphoma that has recurred as diffuse histiocytic lymphoma, the % of ERFC is almost invariably low (table 1). Finally, even in those patients with recurrent nodular disease the % of ERFC appears slightly reduced. The

TABLE 4.—Findings in 6 lymphocytic lymphomas of intermediate differentiation

Patient No.	Tissue	E*	EAC	IgGEA	SIg	Clonality	EAC-FS†	ALP
329	Lymph node	16	80	6	80	MDκ	++++	+
325	Lymph node	21	64	7	50	Gκ	+++	–
311	Lymph node	6	76	16	55	MDκ	++	–
275	Lymph node	25	50	7	61	Mλ	++++	–
228	Lymph node	17	85	17	85	Mκ‡	++	+
	Lymph node	19	86	36	90	MDκ	++	+
277	Lymph node	76	18	2	15	Mκ	+++	+
	Spleen	63	23	16	34	Mκ	+++	+

*Results are expressed as % of positive cells.
†Rosette formation on frozen tissue sections.
‡Not studied for IgD.

T cells within the tumors could be part of the host defense since T-cell infiltrates have been described in a variety of malignant tumors (40).

It is still puzzling that E_N bound relatively poorly to the internodular areas. Histologically these areas are populated by normal-appearing lymphocytes, presumably T cells, since they fail to bind EAC. Activated T lymphocytes have been reported to bind E more readily than T cells that are not stimulated or are not actively participating in an immune response (41). This ready binding has been used as the basis for the active E-rosette test (41). It is conceivable that the cells in the internodular areas are an inactive, residual population which bind E_N poorly. The T cells within the nodules might have been stimulated immunologically and thus may be binding E_N more strongly in the frozen-section assay. These tissues were not assayed in suspension for the active E population. Our studies are preliminary and further work is necessary to determine whether, in patients with nodular lymphoma, a correlation exists between T-cell infiltration and other morphologic and/or clinical parameters.

The immunologic features of nodular lymphoma cells summarized above can be contrasted with those of the cells of well-differentiated lymphoid malignancies. The latter have either a qualitative or quantitative deficiency in complement receptors and poorly express SIg (42). These differences have been related to different B-cell subpopulations (5). Malignant lymphocytic lymphomas of intermediate differentiation (LI) have pathologic features intermediate between those of NPDL and well-differentiated lymphocytic lymphoma (WDL) (3). These tumors usually are diffuse but may have a vaguely nodular pattern. Cytologically there is a population of cells with sparse cytoplasm and nuclei that exhibit a mature clumped chromatin pattern but vary in shape from round to slightly clefted and irregular. Immunologically these tumors also appear intermediate. Table 4 summarizes the data from six cases. All were of B-lymphocytic type. The cells had monoclonal SIg, usually with an IgM heavy chain. In three such cases the neoplastic cells also had IgD. One case had surface IgG. The fluorescent staining was easily seen and of intermediate intensity when compared with NPDL and WDL. The cells also had complement receptors and bound EAC relatively well, both in suspension and on frozen tissue sections. The number of ERFC was in general low, lower than in nodular lymphomas, and was in keeping with the diffuse replacement seen histologically. One case (patient 277) was atypical in that the tissues were only focally involved by the neoplastic process. Both lymph nodes and spleen showed extensive noncaseating granulomatous inflammation. This admixed reactive process probably accounts for the high % of ERFC identified in suspension (table 4). The details of this case are reported elsewhere (43).

The LI tumors were also studied histochemically for the enzymes mentioned above. In three of six cases the cells had surface alkaline phosphatase activity[6] (table 4). This enzyme has also been identified in a small percentage of nodular lymphomas,[6] but is rare in lymphomas of other histologic subtypes. In normal lymph nodes, ALP is found on the membranes of follicular-cuff lymphocytes, but not on lymphoid cells in other areas. Histologically, immunologically, and histochemically, LI tumors thus appear to be truly intermediate between nodular (follicular) lymphomas and WDL. The cells of nodular lymphomas are neoplastic counterparts of follicular B lymphocytes whereas WDL cells are more closely related to medullary-cord B cells. Lymphomas of LI type may derive from B cells of the

[6] Nanba K, Jaffe ES, Braylan RC, et al. Alkaline phosphatase positive malignant lymphomas: a subtype of B cell lymphomas. Submitted for publication.

lymphoid cuff at the margin of follicles and thus exhibit features at the interface between nodular lymphomas and WDL.

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Prognostic Significance of Lymphocytic Surface Markers and Histology in Adult Non-Hodgkin's Lymphoma [1]

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SUMMARY

Neoplastic tissues from 75 adults with non-Hodgkin's malignant lymphoma, histologically classified according to the Rappaport schema, were studied for B- and T-lymphocyte surface markers. All nodular poorly differentiated lymphocytic lymphomas and diffuse well-differentiated lymphocytic lymphomas were B cell. Of 30 diffuse poorly differentiated lymphocytic lymphomas 16 were B, five were T, and nine were "null"; of ten diffuse histiocytic lymphomas, seven were B and three were null. In patients with diffuse lymphoma, those whose malignant cells demonstrated B markers survived significantly longer than those whose malignant cells demonstrated no markers. The prognostic capabilities of the Rappaport histologic classification and surface marker studies were compared. For patients with diffuse lymphomas, classification as B or null more accurately predicted survival than did identification as lymphocytic or histiocytic. However, survival was best predicted by a classification combining the Rappaport histologic scheme with surface marker studies.

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Recent advances in our understanding of the immune system have led to a re-examination of many of the traditional concepts regarding the classification and nomenclature of the non-Hodgkin's malignant lymphomas (NHML). Traditionally, classifications have been based predominantly on histology; terminology has been based on the apparent cellular derivation and degree of differentiation of the malignant cell. The most widely used of the conventional classifications has been that of Rappaport (1); clinicopathologic studies (2–4) have demonstrated its prognostic utility. Recent criticisms (5–7) of the Rappaport classification are based on our improved understanding of lymphocyte differentiation (8,9) and on the demonstration that the so-called histiocyte is often a transformed lymphocyte (7,10,11). It has been suggested (8,12) that future NHML classifications should take into account new immunologic concepts and utilize functional characteristics (ie, surface marker studies) as well as histology.

Several classifications, in particular those of Lukes and Collins (13) and the Kiel classification (10), have been proposed that combine functional and histologic characteristics. However, the prognostic utility of these new classifications has yet to be demonstrated. We have recently found that a classification combining surface marker studies with the Rappaport histologic scheme predicts survival for patients with diffuse NHML better than the Rappaport classification alone (14).

PATIENTS AND METHODS

Seventy-five adults, ≥ 20 years old, with NHML were studied. Initial lymph nodes and other tissues were biopsied and histologically classified according

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to the Rappaport schema (1). Patients were assigned to a clinical stage using the Ann Arbor classification (15). Fifty-nine patients had complete pathologic staging according to the recommendations of the Ann Arbor Conference. Sixteen of the earlier patients were clinically staged but pathologic staging was incomplete, usually because a liver biopsy was not performed in patients who were otherwise stage I–III. Therapy generally consisted of radiation to involved fields for patients who were stage I or II and combination chemotherapy with cyclophosphamide, vincristine, and prednisone for patients who were stage III or IV. Therapy was not determined by histologic classification.

Surface Marker Studies

Malignant tissue from all patients was studied including: involved lymph nodes and other tissue masses in 28 patients, malignant cells from the blood in 35 patients, marrow in 25 patients, pleural or abdominal effusions in four patients, and cerebrospinal fluid in two patients. More than one source of malignant tissue was studied in 27 patients. Tissue was first studied in 48 patients at diagnosis or prior to systemic chemotherapy; 27 patients were first studied at the time of relapse. Eleven patients were studied sequentially; in only one did surface marker studies change. In this patient, $\mu\lambda$ monoclonal surface immunoglobulin (SIg) was present on the malignant cells initially but could not be detected on lymphoma cells studied at relapse following combination chemotherapy.

Suspensions of living cells from blood, bone marrow, body fluids, and lymphoid tissue, collected in the manner previously described, were studied for sheep erythrocyte receptors by rosette formation with unsensitized sheep erythrocytes (E), for SIg by immunofluorescence using monospecific antisera against heavy and light chains, and for complement (C′) receptors by the EAC′ rosette assay (16). When more than one heavy and/or one light chain was found on the surface of lymphoid cells, the cells were treated with polyvalent antiserum, incubated at 37°C for 24 hours, and then studied for reconstituted SIg. In the case of lymph nodes and other tissue masses, cryostat sections were prepared from a portion of the same neoplastic tissue from which suspensions were made (16). These cryostat sections were studied for immunoglobulin by direct immunofluorescence using monospecific antisera, for C′ receptors by the 19S (IgM) EAC′ rosette assay, and for cytophilic antibody (Fc) receptors by the 7S (IgG) EA rosette assay (17).

When studying cell suspensions, we termed as "B cell" those malignancies that demonstrated a clonal proliferation of B cells. For suspensions of unseparated lymphoid cells, a clonal proliferation of B cells was said to be present when $\geq 50\%$ of the lymphoid cells carried on their surface one type of heavy and one type of light chain. For suspensions of cells from blood, which were frequently separated on a Ficoll-Hypaque gradient, a clonal proliferation of B cells was identified when the percentage of B lymphocytes was increased ($> 34\%$) and $\geq 70\%$ of the B cells carried on their surface one type of heavy and one type of light chain. A lymphoma was identified as a "T cell" malignancy when at least 60% E-rosette forming cells were present in a suspension containing $> 50\%$ malignant cells.

Serial cryostat sections were stained with hematoxylin and eosin and with immunofluorescent reagents. In sections histologically involved by lymphoma, the neoplasm was identified as "B cell" when the cells in involved areas showed delicate membrane fluorescence with only one heavy and one light chain. In almost all instances the heavy chain was μ. 19S EAC′ and 7S EA rosette assays were always run in parallel with negative and positive controls for the rosette assay.

We defined as "null cell" those malignancies in which both suspensions of living cells and study of cryostat tissue showed no SIg, sheep erythrocyte receptors, complement receptors, or cytophilic IgG (Fc) receptors.

Statistical Methods

Differences in clinical features between groups of patients were evaluated using the Pearson chi-squared test for percentage differences, and the Mann-Whitney rank test for differences in continuous variables. Differences in survival between groups were evaluated using a Mantel-Haenszel one degree of freedom chi-squared test. The relative prognostic capabilities of the Rappaport classification and surface marker studies were evaluated by multivariate analysis using the Byar exponential survival model (18).

RESULTS

Histologic Classification and Surface Markers

Histologic classification of the 75 tumors according to the criteria of Rappaport demonstrated 32 nodular poorly differentiated lymphocytic lymphomas (PDL-N), 30 diffuse poorly differentiated lymphocytic lymphomas (PDL-D), ten diffuse histiocytic lymphomas (HL-D), and three diffuse well-differentiated lymphocytic lymphomas (WDL-D). None of the patients had undifferentiated (pleomorphic or

TABLE 1.—Results of surface marker studies according to histologic subtypes in NHML

Cell type	No. of patients (%) with histologic subtype—			
	PDL-N	PDL-D	HL-D	WDL-D
B	32 (100)	16 (53)	7 (70)	3 (100)
T	0	5 (17)	0	0
Null	0	9 (30)	3 (30)	0
Total No. of patients studied	32	30	10	3

TABLE 2.—Type of B cell clonal proliferation according to histologic subtype

B cell clonal proliferation	Histologic subtype		
	PDL-N	PDL-D	HL-D
% of patients with—			
μ	90	67	71
$\mu\kappa$	74	75	100
$\mu\lambda$	26	25	—
$\gamma\kappa$	10	33	29
Total No. of patients with SIg+ tumors	30	15	7

Burkitt's) lymphoma. The results of surface marker studies for each histologic subclass are shown in table 1. All cases of PDL-N and WDL-D were B cell (C'+ and/or SIg+); 53% of PDL-D were B cell, 17% were T (E+), and 30% were null (SIg–, E–, C'–, Fc–); 70% of HL-D were B and 30% were null.

Fifty-two tumors were SIg+; the B cell clonal proliferation was either $\mu\kappa$, $\mu\lambda$, or $\gamma\kappa$ (table 2). The most common heavy chain was μ within all three histologic subgroups (PDL-N, PDL-D, and HL-D). In tumors where the heavy chain was μ, the light chain was κ in 75% and λ in 25%. When the heavy chain was γ, the light chain was always κ. There were no statistically significant differences in the frequency of $\mu\kappa$, $\mu\lambda$, or $\gamma\kappa$ clonal proliferation when cases of PDL-N were compared with cases of PDL-D or HL-D. Only three tumors were considered to be B cell lymphomas in the absence of clonal SIg proliferation. In two, SIg was not adequately studied; in one, malignant cells appeared to be SIg–. In all three cases, the EAC' rosette assay for C' receptors was positive while the EA assay for Fc receptors was negative.

Clinical Features

Differences in median age, sex, clinical stage (among those completely staged), symptoms (fever, night sweats, and weight loss) (15), and bone marrow involvement were evaluated among the patients with diffuse lymphoma (PDL-D and HL-D) according to surface marker classification (table 3). Patients with PDL-N and WDL-D were excluded from this analysis since all of them were B cell. Patients with T cell lymphomas were significantly younger than those with null cell ($P < 0.01$) or B cell ($P < 0.05$) tumors. There were no other significant differences among surface marker groups with regard to clinical findings at diagnosis.

Survival

All three patients with WDL-D still survive at 17, 51, and 88 months from diagnosis. Survival curves for the three histologic classes, PDL-N, PDL-D, and HL-D, are shown in figure 1. The current median survival is 46 months for patients with PDL-N, 11 months for patients with PDL-D, and 10 months for patients with HL-D. Patients with PDL-N survived significantly longer than those with PDL-D ($P = 0.00043$) or those with HL-D ($P = 0.00001$). Currently there is no statistically significant difference in survival between patients with PDL-D and HL-D ($P = 0.17$).

Survival curves according to surface marker subgroups for patients with diffuse lymphoma (PDL-D and HL-D) are shown in figure 2. The current median survival is 14 months for patients with B cell lymphomas, 10 months for patients with T cell lymphomas, and 4 months for patients with null cell lymphomas. Patients with B cell lympho-

TABLE 3.—Clinical findings at diagnosis in patients with diffuse lymphoma (PDL-D or HL-D) according to surface marker studies

Clinical finding	Cell type*		
	B (23)	Null (12)	T (5)
Age (yrs)			
Median	57	61.5	29
Range	20–78	45–82	22–59
No. of patients			
Sex (M/F)	10/13	9/3	4/1
Clinical stage			
I–III	1	0	0
IV	17	10	5
Inadequate	5	2	0
Symptoms	8	5	3
Bone marrow involvement	12	6	3

*Nos. in parentheses = total No. of patients.

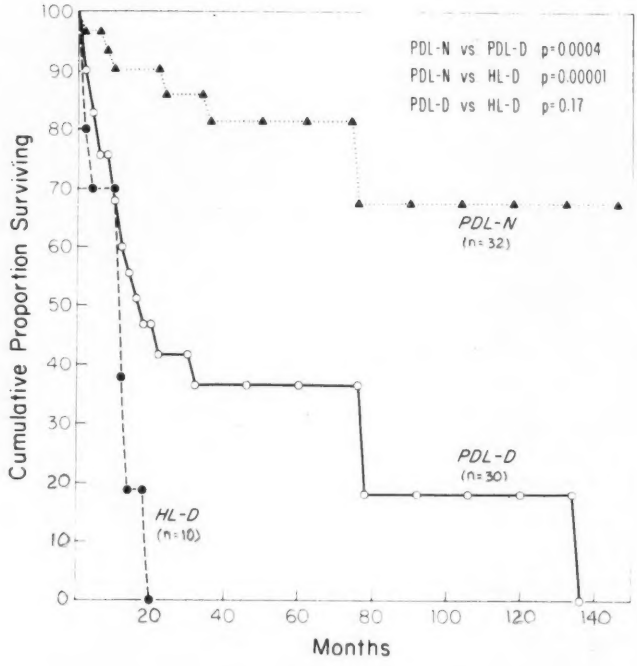

FIGURE 1.—Survival according to the Rappaport histologic classification.

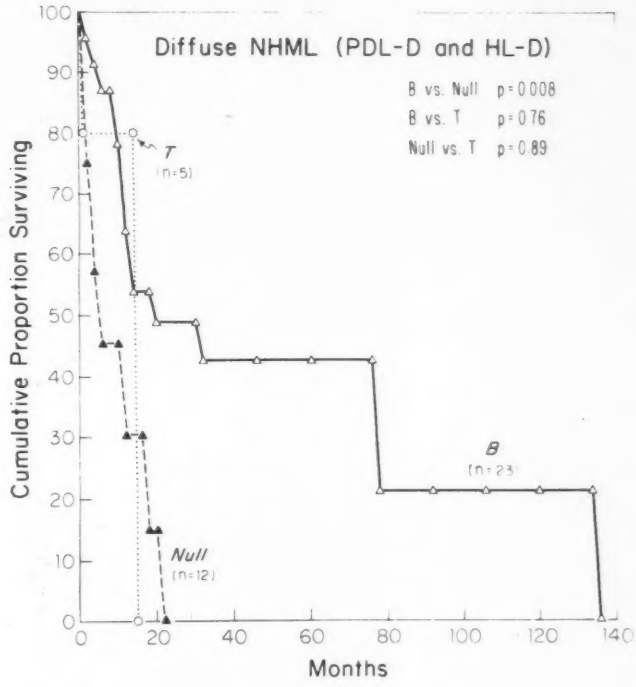

FIGURE 2.—Survival according to surface marker subgroups for adults with diffuse lymphoma classified using the Rappaport schema as PDL-D or HL-D (*from* ref 14).

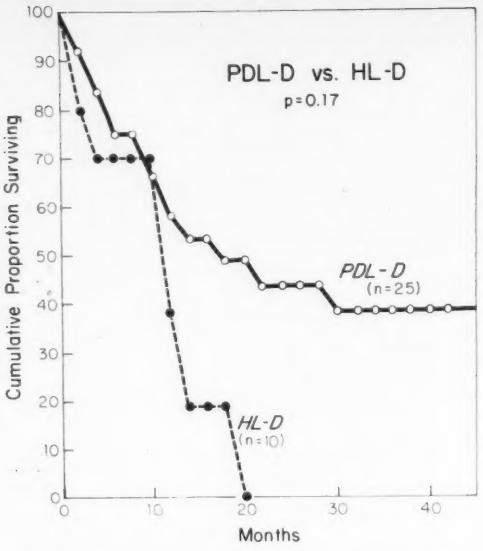

FIGURE 3.—Survival of patients with diffuse lymphoma by histologic type. (Patients with T cell lymphomas have been excluded.)

mas survived significantly longer than those with null cell lymphomas ($P = 0.008$). The difference in survival between patients with B cell lymphomas and those with null cell lymphomas could not be accounted for by any of the factors (2) known to have prognostic significance in NHML. Among patients with B cell lymphomas there were no significant differences in survival relative to whether the clonal proliferation was $\mu\kappa$, $\mu\lambda$, or $\gamma\kappa$ (table 4).

The prognostic capabilities of surface marker identification as B or null, and histologic classification as histiocytic or lymphocytic, for patients with diffuse lymphoma (PDL-D and HL-D), were compared using a multivariate analysis (18). Since only five patients with T cell lymphoma were studied, they were excluded from this analysis. Multivariate analysis revealed that surface marker identification was more useful than histologic classification in predicting survival. This is suggested by conventional life-table analysis (figs 3 and 4). Figure 3 shows survival curves for the patients with diffuse lymphoma when they are grouped according to the Rappaport histologic classification as PDL-D or HL-D. Figure 4 shows survival curves for the same patients grouped according to surface marker characteristics as B or null.

For patients with diffuse lymphoma, classification as B or null cell appears to have more prognostic utility than designation as histiocytic or lymphocytic; however, prediction of survival is significantly ($P < 0.025$) improved by using both histology and surface marker classification. In the multivariate analysis, combining histology and surface marker data increased the likelihood ratio by 2.965, which is equivalent to a one degree of freedom chi-square

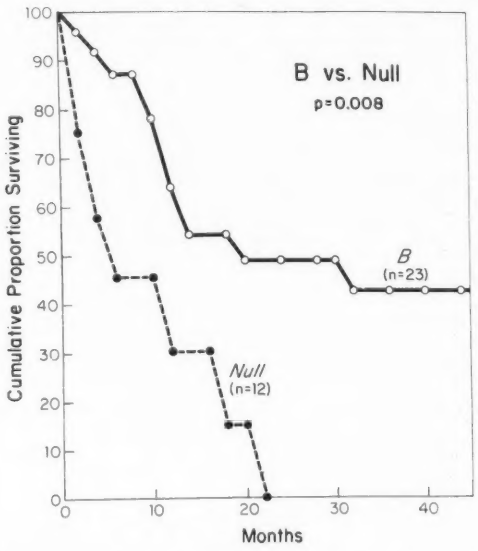

FIGURE 4.—Survival according to surface marker classification (same population as in fig 3).

TABLE 4.—Median survival in months by type of B cell clonal proliferation

B cell clonal proliferation	Survival (mos) with histologic subtype—*		
	PDL-N (30)	PDL-D (15)	HL-D (7)
μ	35+	36+	12+
$\mu\kappa$	33+	42+	—
$\mu\lambda$	52+	22	—
$\gamma\kappa$	51+	11	11

*Nos. in parentheses = total No. of patients.

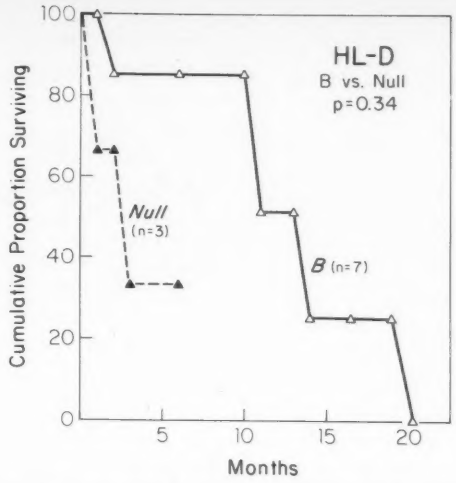

FIGURE 5.—Survival according to surface markers for patients with HL-D.

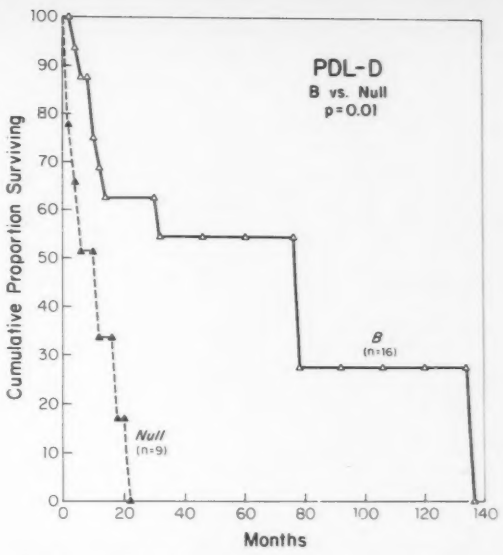

FIGURE 6.—Survival according to surface markers for patients with PDL-D.

of 5.930. This improvement in survival prediction by combining classifications is also suggested by conventional life-table analysis (figs 5 and 6). Within both histologic groups (HL-D and PDL-D), patients with B cell lymphomas survive longer than those with null cell lymphomas. Current median survival is 26 months for patients with B cell PDL-D, 11 months for those with B cell HL-D, 5 months for those with null cell PDL-D, and 3 months for those with null cell HL-D.

DISCUSSION

Many studies of lymphocyte surface markers in NHML have appeared in recent years. In accord with the results reported here, these have usually demonstrated that PDL-N and WDL-D are B cell malignancies (17,19,20) but that PDL-D and HL-D may be B, null, or T cell (11,21–26). Although occasional investigators (24) have commented upon the short survival of specific patients with null cell lymphomas, to date only our study of adult NHML has correlated surface markers with survival (14). In contrast, in the childhood lymphoproliferative disorders (acute lymphocytic leukemia and lymphoma) several studies have demonstrated the value of surface markers in predicting survival (27–29).

To be useful to the clinician, a classification should identify groups of patients with different clinical courses and response to treatment, and should be convenient for pathologists to apply in their everyday diagnostic work. The Rappaport histologic classification for NHML has fulfilled both of these criteria. However, even though clinicopathologic studies evaluating the prognostic utility of the Rappaport classification have shown marked differences in survival between patients with diffuse and nodular lymphoma (2–4), this study and a number of others (2–4) have not found statistically significant differences in survival between patients with HL-D and PDL-D.

In contrast to histologic subdivision, surface marker classification of diffuse lymphomas identifies two groups of patients whose survival is statistically different. Patients whose malignant cells demonstrate B markers survive significantly longer than those whose malignant cells demonstrate no markers. The reason for this difference is unclear. None of the prognostic factors known to influence survival in NHML (2) differed significantly between surface marker groups. While surface markers appear to give more prognostic information, the present study also suggests that a classification combining lymphocyte surface markers with histology gives the best prediction of survival in adults with diffuse NHML.

Many sophisticated techniques are now available to study lymphocyte surface markers, and study of additional surface markers may add further prognostic information. The classification used here, a

combination of the Rappaport histologic schema with surface marker studies, has the following advantages: (*a*) it improves prediction of survival over histologic classification alone, (*b*) it appears to be practical and readily usable, and finally (*c*) it takes into consideration new functional concepts. Preliminary data also suggest that it may be useful in selecting therapeutic regimens for individual patients.

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Lukes-Collins Classification and Its Significance[1]

Robert J. Lukes[2,*] and Robert D. Collins[3]

SUMMARY

This paper summarizes the combined results of the multiparameter study of 384 cases of malignant lymphoma and related leukemias by the investigative groups from Vanderbilt University and the University of Southern California medical schools. There were 256 cases of the B cell group, 59 T cell, 65 U cell (undefined), and four histiocytic. The results demonstrate that, with the exception of the rare true histiocytic lymphoma and a portion of acute lymphocytic lymphoma, the lymphomas mark as T or B cell types and the morphologic features are predictive of the specific type. These results support the authors' original proposals that (*a*) lymphomas involve principally the T and B cell systems; (*b*) nodular lymphomas are lymphomatous follicles composed of follicular center cells and B cell lymphomas; and (*c*) with rare exceptions the histiocytic type of Rappaport consists of transformed lymphocytes of either B or T cell types. Comparison of these results with traditional cytologic types reveals that the cell populations in acute lymphocytic leukemia, chronic lymphocytic leukemia, and most of the cytologic types of Rappaport are heterogeneous, and this undoubtedly accounts for the diversity of their clinical expressions and the varied responses to therapy. The identification of more homogeneous cytologic types using the functional approach suggests the existence of a number of distinctive clinical-morphologic-immunologic entities, such as the convoluted T cell and the immunoblastic sarcoma of the B and T cell types. The redefinition of these disorders using a functional approach provides a sound conceptual basis for further investigation and elucidation of the basic biology of lymphomas. Undoubtedly it will lead to a better understanding of these previously bewildering proliferative disorders and possibly even a redesign of therapeutic approaches.

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The malignant lymphomas now appear to be accepted as neoplasms of the immune system (1,2). The terminologies and classifications of the past, including that of Rappaport (3), were proposed long before the remarkable developments in immunology of the past decade, and therefore do not reflect our modern understanding of this special area.

In 1971 we proposed a new immunologic approach to the malignant lymphomas relating them to the T and B cell systems and to alterations in lymphocyte transformation whereby lymphomas may develop through either a block or a "switch-on" (derepression) in transformation. We also proposed that the follicular center is the site of B cell transformation, that nodular lymphomas are lymphomatous follicles and involved follicular center cells (FCC), and that, with rare exceptions, the histiocytic lymphomas of Rappaport are lymphomas of transformed lymphocytes (4,5). This proposal was elaborated upon at a series of international meetings in 1972 and 1973; a functional classification was proposed, and a multiparameter investigative approach was outlined for the morphologic, cytochemical, and immunologic redefinition of the lymphomas (6–8).

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In the intervening years a number of reports have supported the above proposals. The Vanderbilt University Group,[4] under Dr. Collins, demonstrated that FCC lymphomas had the surface markers of B cells (9), and, in an ultrastructural study, demonstrated that the cleaved and noncleaved (transformed) FCC lymphoma cells in both follicular and diffuse proliferations were indistinguishable from the cells of normal follicular centers (10).

Using the Rappaport classification (3), Aisenberg and Long (11) and Brouet et al (12) also showed that the lymphoma cells in most of their cases marked as B cells. Lennert (13) had insisted that nodular lymphomas were of follicular lymphomas and Kojima et al (14) provided strong evidence of this association by demonstrating desmosomes on dendritic reticulum cells in follicular lymphomas similar to those seen in normal follicles. Jaffe and associates, in their beautiful study using the frozen section sheep erythrocyte rosette (EAC) technique (summarized elsewhere in this issue), provided convincing support for the follicular nature of nodular lymphomas.

In 1973, parallel multiparameter investigative programs were developed by the investigative groups at Vanderbilt University and the University of Southern California[5] medical schools. In this presentation we will report the combined general results from these two groups concerning the morphologic, cytochemical, ultrastructural, and immunologic surface marker studies of 384 cases of non-Hodgkin's lymphomas and related leukemic disorders. The results of this study provide strong support for our above proposals. Subsequently, each investigative group will publish detailed reports of specific cytologic types.

METHODS AND MATERIALS

Before therapy, material for the multiparameter studies was collected from lymph node biopsies, spleen, bone marrow, or peripheral blood. Frequently, during relapse, followup specimens were obtained for comparative evaluation, often from spinal fluid, pleural fluid, or even peritoneal fluid, and from some of the above sites. Of the 384 cases in this study, 186 were studied by the Vanderbilt University Group and 198 by the University of Southern California Group. The cases evaluated by the former group were collected from the Vanderbilt University Hospital and the associated Veterans' Administration Hospital, and those of the University of Southern California Group were obtained from the Los Angeles County-University of Southern California Medical Center, the Childrens Hospital of Los Angeles, and the participating hospitals of the Southern California Lymphoma Group which now includes 20 major hospitals. Cell suspensions were prepared by the Ficoll-Hypaque method. Sheep erythrocyte rosette techniques (E, EAC, EA) were performed on the suspended cells using the method of Jondal et al (15) and the surface immunoglobulins were determined using the immunofluorescent-labelled monospecific antiglobulin. Tissue imprints or smears were prepared in parallel from the various specimens and a variety of routine techniques were applied, including the Wright's stain, the periodic acid-Schiff, methyl green pyronine, granulocyte stains (peroxidase, Sudan black, and chloroacetate esterase), the acid phosphatase with and without tartrate, and the nonspecific esterase (alpha naphthyl butyrate) for histiocytes. Representative specimens were collected in glutaraldehyde on every case and processed for ultrastructural studies using conventional electron microscopy. The immunoperoxidase technique for cytoplasmic immunoglobulin was performed on selected cases using the technique of Taylor and Mason (16).

Tissue was collected and processed for histologic evaluation under ideal conditions and reviewed and interpreted without knowledge of the results of the above studies in order to determine the significance and reliability of the morphologic criteria.

MORPHOLOGIC AND CONCEPTUAL BASIS

The basis for our approach has been presented in detail elsewhere (4–8). Briefly summarized, the new functional approach is based upon (*a*) extensive morphologic experience as a consultant reviewing large numbers of cases of non-Hodgkin's lymphomas and a systematic review of our own institution's cases; (*b*) experience with the morphologic expressions of in vitro lymphocyte transformation in both smears and sections; and (*c*) comparative camera lucidas study of normal follicular centers and nodular lymphomas. From the latter it was apparent that both the normal follicular centers and the lymphomatous nodules were composed of cleaved and noncleaved cells of varying sizes and proportions along with dendritic reticulum cells. The Vanderbilt University Group's comparative ultrastructural study (10) has since confirmed the similarities between normal FCCs and lymphoma cells of nodular lymphomas. This study also revealed that diffuse

[4]Members of the investigative group from the Vanderbilt University School of Medicine are: James Leech, John Flexner, Alan Glick, Jim Waldron, and Robert Collins.

[5]The University of Southern California School of Medicine team is composed of John Parker, Clive Taylor, Barbara Tindle, Paul Pattengale, Thomas Lincoln, Stebbins Chandor, Arthur Williams, and Robert Lukes.

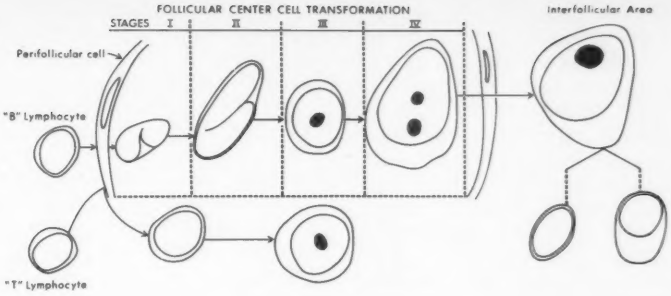

FIGURE 1.—Development of malignant lymphomas of FCCs.

lymphomatous proliferations contained similar FCCs. The observed resemblance of normal noncleaved FCCs and in vitro transformed lymphocytes led us to propose that most tumors interpreted as histiocytic lymphomas or reticulum cell sarcomas in the past were lymphomas of transformed lymphocytes of either B or T cell types.

From the above observations and the general agreement that follicular centers are composed of B cells, we proposed that the follicular center was a site of B cell transformation and that FCCs were precursor cells of plasma cells. Figure 1 shows the proposed sequence of transformation in the follicular center. Under the influence of antigen on the surface of a dendritic reticulum cell, the small round lymphocyte (B cell) of the lymphocytic mantle passes through the following stages: 1, small cleaved; 2, large cleaved; 3, small noncleaved; and 4, large noncleaved.

The noncleaved cells are similar to the in vitro transformed lymphocytes and are the dividing cells of the follicular center, while the cleaved cells and the small lymphocytes of the lymphocytic mantle appear to be essentially nondividing cells. The noncleaved or transformed FCCs at times seem to move out of the normal follicular center into the lymphocytic mantle and the interfollicular tissue where they are designated as immunoblasts of B cells. They may continue to divide and form daughter precursor cells of plasma cells; alternately, if no additional (antibody) plasma cells are needed, they may revert to small lymphocytes capable of subsequent immediate response to another challenge by the same antigen and produce transformed lymphocytes and plasma cells, but without forming follicles. The transformation of T cells apparently takes place in a parallel fashion outside the follicular center without forming cleaved FCCs or plasma cells.

The cells shown in the sequences of B and T cell transformation (fig 1) form the basis of our functional classification, except for the convoluted lymphocyte and the Sézary cell. The convoluted lymphocytic lymphoma appears to arise from an abnormality in T cell development. The relative position of the Sézary cell in our classification is uncertain, although Broder et al (17) have recently suggested that it is a lymphoma of helper T cells. The remaining cytologic types can be related to the various stages of transformation in the two systems, and possibly they develop through a block or a "switch-on" in the transformation of T or B cells. A block at the level of the small B lymphocytes results in an absence of small cleaved FCCs and an apparent inability to form follicular centers, plasma cells, or antibodies; these findings are all characteristic of chronic lymphocytic leukemia of B cells or its lymph node counterpart, the lymphoma of small B lymphocytes.

A block at the next position results in a small cleaved FCC population, usually with some degree of follicle formation, apparently because these cells retain their ability to form follicles. A block at the next position produces a lymphoma of larger cleaved cells, often with extreme variations in nuclear configurations; follicle formation is less common and there is usually some degree of sclerosis. The cleaved FCC lymphomas usually have few intermixed, noncleaved, or transformed FCCs, although occasionally the proportion of large transformed cells approaches 20%. Mitoses are usually rare. The next two positions represent a "switch-on" (derepression) of FCC transformation to the dividing cells of the follicular center. The small noncleaved (transformed) FCCs fulfill the cytologic criteria for the Burkitt lymphoma when they are uniform in size. Recently, the observation that a small proportion of these cases have a partially follicular pattern (18) has provided further support for their FCC origin. However, the nuclear size of the small transformed FCC usually shows considerable variation, and this variant is commonly desig-

nated as the non-Burkitt type. Both the Burkitt and the non-Burkitt types are made up of relatively small pyroninophilic cytoplasmic cells with nuclei that are generally smaller than the "starry-sky" phagocyte nucleus. Both are included in the small transformed (noncleaved) FCC type. The large transformed (noncleaved) FCCs consist of a similar type of proliferation but of larger cells. The transformed FCC lymphomas, whether made up of predominantly small or large cells, only occasionally exhibit some degree of follicle formation. The transformed B cell lymphoma arising in the interfollicular tissue has been designated an immunoblastic sarcoma of B cells; it does not form follicles and often exhibits plasmacytoid features. The proliferative turnover rate is high and aggressive, and the mitoses are numerous. This picture frequently develops in chronic abnormal or defective immune states such as that in the immunosuppressed patient with a graft rejection, malabsorption syndromes with alpha-chain disease, or nontropical sprue, Hashimoto's disease, Sjögren's syndrome, Waldenström's macroglobulinemia, and a variety of other disorders, including senescence which appears to represent an immune deficiency state. The large cleaved FCCs, the transformed FCCs, and the immunoblasts of B cells, both normal and lymphomatous, all have cytoplasmic immunoglobin which has been demonstrated by the immunoperoxidase stain for monospecific immunoglobulin (19).

In the T cell sequence, proliferation occurs outside the follicular center in the paracortical region. The small-lymphocyte lymphoma of T cells resembles its counterpart in the B cell sequence in size, but may exhibit considerable nuclear irregularity. The immunoblastic sarcoma of T cells shows a wide range of nuclear size and usually has abundant pale-staining cytoplasm that is generally less pyroninophilic. The cells lack plasmacytoid features and do not form follicles. Often this sarcoma is associated with a peculiar irregular small lymphocyte which is distinguishable from the cleaved FCCs and probably represents a lymphomatous T cell. This peculiar lymphocyte resembles the lymphocyte found in Lennert's lymphoma (20) which has an associated epithelioid component. In the three cases with multiparameter studies included in this report these peculiar lymphocytes form spontaneous E rosettes, and the process appears to represent a special T cell lymphoma. Our study appears to establish the convoluted lymphocytic lymphoma as a T cell lymphoma, and this tumor may represent an abnormality in the development of T cells. The origin of the Sézary cell and the closely related cells of mycosis fungoides is uncertain, although it is generally accepted that both are of T cell type. The large cells of mycosis fungoides, in the tumor phase, may represent large transformed T cells and may constitute an immunoblastic sarcoma of T cells.

FUNCTIONAL CLASSIFICATION

Figure 2 lists the cytologic types in our functional classification of malignant lymphoma; these have been described in detail previously (6–8). The only additional type introduced into the classification since our original publications is the lymphoma of the small lymphocyte of T cells which has been confirmed in our laboratories. We regard the small lymphocyte of B cells as the tissue manifestation of chronic lymphocytic leukemia (CLL) of B cells, but at times this may not express itself in the bone marrow or peripheral blood.

Our classification consists of four general groups: (1) the U cell (or undefined cell), (2) the T cell, (3) the B cell, and (4) the true histiocyte. The U cell was created to accommodate those cells which existing techniques cannot mark specifically. Recent studies suggest that specific anti-B cell serum will mark as special B cells most of the unmarked cells encountered in acute lymphocytic leukemia (ALL), as reported by Winchester et al (21) and Schlossman et al (22). It remains to be determined whether any of these primitive-appearing cells will remain unmarked and whether the null cell is merely a special B cell of the marrow.

Both the T and B cell groups contain a lymphoma of small lymphocytes and one of large transformed lymphocytes (immunoblastic sarcoma). The remaining T cell types are represented by the primitive-appearing convoluted lymphocyte and the cerebriform cell of Sézary's syndrome and of mycosis fungoides. The remaining B cell types are represented by the FCC types found as plasma cell

- U cell (undefined)
- T cell
  - Small lymphocyte
  - Convoluted lymphocyte
  - Sézary cell–mycosis fungoides
  - Immunoblastic sarcoma
  - Lennert's lymphoma
- B cell
  - Small lymphocyte
  - Plasmacytoid lymphocyte
  - FCC
    - Follicular or diffuse, with or without sclerosis
      - Small cleaved
      - Large cleaved
      - Small transformed (noncleaved)
      - Large transformed (noncleaved)
  - Immunoblastic sarcoma
  - Hairy cell leukemia
- Histiocytic

FIGURE 2.—Functional classification of malignant lymphoma.

precursors, and the plasmacytoid lymphocyte commonly seen with Waldenström's macroglobulinemia, but also seen with IgG monoclonal gammopathy, or at times without a serum gammopathy. The noncleaved FCC types are regarded as synonymous with transformed FCCs.

RESULTS

Tables 1, 2, and 3 summarize the results of our combined studies of 384 cases of non-Hodgkin's lymphomas and related leukemias. In general, the lymphomas and the related leukemias, with the exception of a portion of ALL in the U cell group and four cases with histiocytic markers, can be related to the T and B cell systems. Sixty-five cases (17%) were in the U cell group, 59 (15%) in the T cell group, 256 (67%) in the B cell group, and four (1%) in the histiocytic group. Of the 384 cases in the series, > 90% had an adequate number of cells for evaluation. Cells were insufficient in number for study when the specimen was inadequate in size or when a large proportion of the cells were dead or dying when tested by the trypan blue exclusion method. This latter situation was most common in proliferations with high turnover rates such as the large transformed FCC, immunoblastic sarcoma of T and B cell types, and also the large cleaved FCC type associated with sclerosis (here it seems difficult to separate out the cells).

U Cell (Undefined)

The 65 cases in this group had ALL of childhood. In this group only a small number of cells had surface immunoglobulin or formed E rosettes. Using the cytocentrifuge, however, we were able to demonstrate E rosette formation about the leukemic cells in 14 cases; this is presumptive evidence of their T cell origin, even though the recorded frequency ranged from 1% to 20%. This observation is of considerable importance because Prof. Seligmann (personal communication) has indicated that when leukemic cells form E rosettes, his anti-T cell serum marks such cells as T cells. We do not yet know the clinical and therapeutic significance of a number of T cells < 20%, hence these 14 cases are included arbitrarily in the U cell group, though eventually these cases may be included in the T cell portion of ALL. This study will be reported in detail elsewhere.[6]

TABLE 1.—Functional study population by cytologic type

	No. of cases	
U cell (undefined)	65	
T cell		
Small lymphocyte	3	
Convoluted lymphocyte	26	
Sézary-mycosis fungoides	6	
Immunoblastic sarcoma	21	
Lennert's lymphoma	3	
Total	59	
B cell		
Small lymphocyte	80	
Plasmacytoid lymphocyte	14	
FCC		
Small cleaved	60	
Large cleaved	32	130
Small transformed (noncleaved)	22	
Large transformed (noncleaved)	16	
Immunoblastic sarcoma	15	
Hairy cell leukemia	17	
Total	256	
Histiocytic	4	
Total	384	

[6]Williams AH, Taylor CR, Higgins GR, et al. Childhood leukemia and lymphoma. I. Correlation of morphology and functional studies. Submitted for publication to *Cancer*.

TABLE 2.—Immunologic surface marker studies: B cell lymphomas

	No. of cases	Insufficient cells	Clonality (%)			Immunoglobulin low
			Mono	Bitypic	Poly	
Small lymphocytes	80	2	70	0	13	17
Plasmacytoid lymphocytes	14	2	50	0	25	25
Small cleaved-FCCs	60	8	79	6	3	12
Large cleaved-FCCs	32	9	74	4	9	13
Small transformed-FCCs	22	4	67	22	11	0
Large transformed-FCCs	16	5	73	0	0	27
Immunoblastic sarcoma	15	2	62	0	7	31
Hairy cell leukemia	17	2	57	14	14	14
Total	256					

TABLE 3.—Childhood lymphomas and leukemias

	No. of cases studied
U cell (undefined) (includes 14 cases with < 20% rosettes)	65
T cell	
Convoluted lymphocyte	13
B cell	
Small transformed (noncleaved) FCC diffuse	6
Total	84

T Cell

Of the 59 cases exhibiting the morphologic features of T cells, enough cells for study were obtained in 57 (97%). In most cases the proportion of E rosettes ranged from 50% to 90%. However, we consider the formation of E rosettes in cytocentrifuge preparations to be essential to the demonstration of T cell origin. Thus, all 26 cases of the convoluted type were acceptable, even though the proportion of E rosettes was < 20% in 10 cases because the convoluted lymphocytes were observed to form E rosettes. In general, only a few cells showed surface immunoglobulin. In the immunoblastic sarcoma and the convoluted lymphocytic groups, > 20% of cells in three cases in each group had polyclonal surface immunoglobulin which was interpreted as an autoantibody response. This experience with 59 cases of T cell lymphoma strongly suggests that it is the demonstration of E rosette formation by the lymphoma cells in the cytocentrifuge preparations which is critical and that the number of rosettes is much less important. We also encountered three cases of a distinctive lymphocytic lymphoma associated with clusters of epithelioid histiocytes similar to the type described by Lennert et al (20).

B Cell

Table 1 lists the distribution of the cases in the B cell group and table 2 gives the detailed results of the surface immunoglobulin studies. Of the 256 B cell cases, 130 (51%) exhibited morphologic features of FCCs; cells of the next largest group, 80 cases, were classified as small B cell lymphocytes. There were also 14 cases of the plasmacytoid lymphocytic type, 15 immunoblastic sarcomas of B cells, and 17 hairy cell leukemias. There were not enough cells for study in 34 cases (13%) of the B cell group. Sufficient cells were difficult to obtain most commonly in the large cleaved FCC group, possibly because of associated sclerosis and as a consequence of poor cell separation. Cell death was common in cases with the large transformed FCC type and almost one third of these had insufficient numbers of cells for study. Monoclonal surface immunoglobulins were demonstrated in most cases in each cytologic type with a frequency ranging from 50% to 79%. The small cleaved FCC type showed the highest frequency. The plasmacytoid group showed the lowest frequency (50%); apparently the more mature plasmacytoid cells secrete immunoglobulin but frequently do not carry it on the cell surface. "Bitypia" of surface immunoglobulins, ie, the demonstration of a high frequency of heavy chain and both kappa and lambda light chains, was observed in four types of B cell lymphomas; it was rare with the small and large cleaved FCC types, but was seen in 14% of the hairy cell cases and 22% of the small transformed FCC cases. Bitypia may result from a crossover in antibody reaction and probably is related to monoclonality. Polyclonal surface immunoglobulin was detected in 3%–25% of all cytologic types except for the large transformed FCCs. In a high proportion of cells, such immunoglobulin exhibited a distinctive fluorescent pattern, which suggests an auto-antibody reaction. With the exception of the small transformed FCC type, a small proportion of all cases had only a few cells which exhibited surface immunoglobulin. This finding may indicate that at times lymphoma cells of B cell type may be unable to produce immunoglobulin and secrete it on to the surface. The B lymphoma cells did not exhibit E rosette formation in cytocentrifuge preparations. In general, there is clear evidence that all the cytologic types of B cell lymphomas, including the FCC types we described, produce monoclonal immunoglobulin and exhibit it on their surface as evidence of their origin in B cells. We have included hairy cell leukemia in the B cell group because seven of the 15 cases that provided sufficient cells for study exhibited monoclonal surface immunoglobulins. The Vanderbilt University Group also has demonstrated monoclonal immunoglobulin synthesis in three cases after removal of the surface immunoglobulin by trypsinization.

Histiocytic

Only four of the 384 cases of this study were characterized as the histiocytic type. These cells, identified using the alpha naphthyl butyrate cytochemical stain, failed to form E rosettes or produce evidence of surface immunoglobulin.

CHILDHOOD LYMPHOMAS AND LEUKEMIAS

Table 3 lists the results of the prospective study of childhood lymphomas and leukemias together

because our recent retrospective study of 114 cases from the Childrens Hospital of Los Angeles[7] demonstrated that leukemia and childhood lymphoma have common manifestations. Of the 84 cases, 13 were of the T cell group and all were of the convoluted lymphocytic type; six were in the B cell group and all were of the small transformed FCC diffuse type; 65 were in the U cell (undefined) group. As indicated earlier, 14 cases of the U cell group had < 20% E rosettes; we also demonstrated that in the cytocentrifuge the leukemic cells formed E rosettes. Until their clinical relevance is ascertained, these cases are included in the U cell group because of the low frequency of E rosette formation, even though such cases will probably be included in the T cell group eventually. This study demonstrates the heterogeneity of ALL and the close interrelationship of lymphomas and the leukemias of childhood.

MORPHOLOGIC OBSERVATIONS

The application of morphologic criteria to the cytologic types we described earlier (6,8) gives a high degree of correlation with the results of the functional study. As we have accumulated cases, we have clarified areas of uncertainty such as immunoblastic sarcoma of T cells and histiocytic lymphoma, and we have sharpened the criteria for these more recently recognized types. Histiocytic lymphoma at times contains histiocytes which have an abundant cytoplasm and also monomorphous areas of monocytes, both lacking neoplastic features. Such proliferations may resemble malignant histiocytosis. The evidence obtained from this study suggests that the results of functional studies can be predicted from the morphologic features of the cytologic types.

DISCUSSION

This multiparameter study of 384 cases of non-Hodgkin's lymphoma and related leukemias provides strong support for our original proposal that (*a*) these disorders can be related to the T and B cell systems; (*b*) nodular lymphomas involve lymphomatous follicles and FCCs in the B cell system; (*c*) malignant lymphomas involve alterations of lymphocyte transformation; and finally (*d*) lymphomas of the histiocytic type of Rappaport (with rare exceptions) are transformed lymphocytes of T or B cell systems. Of major importance, we have demonstrated that the cytologic types of our classification of malignant lymphoma (6–8) can be used to predict the results of the multiparameter studies and to demonstrate their cell of origin—whether T or B cell or histiocytic. The new classifications subsequently proposed by others and reviewed by Dorfman elsewhere in this symposium indicated, however, that it is premature or inappropriate to relate malignant lymphomas to modern immunologic progress and to base the classification of malignant lymphomas on the T and B cell systems. However, all of these classifications, except the Kiel scheme, are slight modifications of the Rappaport classification, and during this symposium Rappaport acknowledged the need for changes by adding four new cytologic types to his own classification.

The results of this study conclusively demonstrate that the non-Hodgkin's lymphomas and related leukemias mark as T or B cells with the exception of a few cases of histiocytic lymphoma of Rappaport (3) and a component of ALL of the U cell (undefined) type in our classification. Recent studies employing a possibly specific anti-B cell serum suggest that even this portion of ALL represents a special B cell type while the remainder of ALL involves T cells (22) (Seligmann M, personal communication).

It seems likely that the development of new technical improvements, particularly the highly specific anti-T and anti-B cell serums, will eliminate some of the reported inconsistencies, such as unmarked lymphoma cells or those with a high incidence of polyclonal surface immunoglobulins. Our demonstration of E rosette formation about leukemic cells in the cytocentrifuge preparations appears to show that the cases of ALL with frequency of E rosettes < 20% are of T cell type. This view is supported by Seligmann's observation that cases of ALL with a low incidence of E rosette formation will mark with his anti-T cell serum if it can be demonstrated morphologically that the leukemic cells form E rosettes (Seligmann M, personal communication). Our study reaffirms the importance of the morphologic features of the lymphoma cells and the importance of studies in which multiparameter techniques are used as cross-checks. Thus, the four cases in the histiocytic group not only lack the monoclonal surface immunoglobulin of B cell types and E rosette formation of T cells, but exhibit the histiocyte enzyme demonstrated cytochemically by the alpha naphthyl butyrate technique.

The demonstration that most lymphomas involve the T and B cell systems and are neoplasms of the immune system has far-reaching implications. It calls for a major change in the manner in which lymph node biopsies and other tissues are collected and processed so that we can effectively demonstrate the cytologic features of lymphoma cells. In

[7]Schneider BK, Higgins GR, Swanson V, et al. Malignant lymphomas of childhood. Submitted for publication.

the future, pathologists will need to collect fresh tissue in order to make tissue imprints and achieve ideal fixation. No longer can we drop intact, uncut lymph nodes or spleen into formalin, to be examined and prepared for processing hours later or on the next day; such a practice delays the penetration of the fixative, produces partial autolysis of much of the tissue, and causes marked cytologic alteration centrally. All of these changes interfere with satisfactory cytologic evaluation and identification.

For his part, the clinician must recognize the heterogeneity of cytologic types represented in the past classifications of malignant lymphoma, of ALL and CLL, and particularly of the histiocytic lymphoma, the poorly differentiated lymphocytic lymphoma, and the mixed types of Rappaport (3). Undoubtedly this heterogeneity accounts for the diverse clinical expressions and varied responses to therapy. The heterogeneity of ALL is now generally acknowledged; we now believe this group includes the unmarked cases (U cell) and the B cell and T cell types of ALL. Even the T cell type of ALL appears to be heterogeneous and includes the convoluted lymphocytic lymphoma-leukemia we have described (23). In contrast to the unmarked cell types, both T cell leukemia and the closely related convoluted lymphocytic type relapse early on the usual ALL therapy. This fact and the recently demonstrated dependence on L-asparagine of T cell leukemia and lack of dependence of the unmarked type further illustrate the heterogeneity of ALL (24). Clinicians should also appreciate that our new functional approach permits us to recognize homogeneous cytologic types, such as the convoluted lymphocytic T cell type which is emerging as a distinctive clinical-morphologic-immunologic entity (23). This type (observed predominantly in children, commonly in teenagers) shows a definite male preponderance, and frequently presents with a mediastinal mass; it shows a dramatic response to conventional ALL therapy and usually relapses rapidly in the marrow and central nervous system. In the past, depending upon the dominant clinical presentation, the convoluted T cell has been classified either with ALL or variably within the cytologic types of lymphoma. Our recent retrospective study of 114 cases of childhood lymphomas from the Childrens Hospital of Los Angeles has demonstrated the importance of the convoluted lymphocytic type and the significance of the cytologic types delineated in the functional classification (*see* footnote 7). The convoluted lymphocytic type was observed in 56 children (49%); they exhibited a strikingly different clinical presentation from those with the major B cell type, the 46 children (40%) with the small transformed (noncleaved) FCC type. Of the convoluted lymphocytic cases, the predominant presentation was mediastinal mass in 52%, a lymph node enlargement in 16%, and lytic bone lesions in 20%. Of those with the small transformed FCC type, 72% presented with an abdominal mass and rarely with a mediastinal mass, lymph node, or bone lesion. During relapse of the disease, 60% of those with convoluted T cell lymphocytic disease and 35% of those with small transformed FCC type developed a diffuse leukemic type of marrow involvement. This retrospective study demonstrates that our functional approach provides a meaningful classification of the lymphomas of childhood. It has established the convoluted lymphocytic type as a distinctive homogeneous T cell type with a characteristic clinical presentation. The non-Hodgkin's lymphomas clearly are not a single disease, but are a group of disorders principally of the T and B cell systems. They may include as many as ten distinctive clinical-morphologic-immunologic variants which are related either to the position of the cell of origin in lymphocyte transformation in the T and B cell systems or to abnormalities in the development of T and B cells. The clear delineation of these entities awaits both a large retrospective study in adults and further detailed clinical-morphologic-functional correlations.

The demonstration that lymphomas of the T and B cell system are neoplasms of the immune system provides a sound conceptual basis for investigation and it has important implications for diagnosis and the design of therapeutic approaches. We believe that the various subtypes of malignant lymphomas of the T and B cell systems represent aggregates of immune defective cells which differ in varying degrees from their normal counterparts. They appear to arise during abnormal immune processes in the respective T and B cell tissues and, like their normal counterparts, migrate, target, and function with varying degrees of activity. If some lymphomas arise, as we have proposed, as a block or a "switch-on" in lymphocyte transformation and represent clonal expressions of positions in lymphocyte transformation in the T and B cell system, we are presented with an extraordinary opportunity to elucidate the normal sequence of T and B cell transformation and to design therapeutic interventions to correct the transformation defects. Similarly, if the convoluted lymphocyte represents, as we propose, a defect in T cell development, investigation of variants of this lymphoma may permit us to reconstruct the sequences in T cell development and also to design corrective therapy. An improved understanding of the basic process and further progress in the definition of the defective character of lymphoma cells will make more urgent the need

to develop additional and more specific techniques to identify and characterize normal and lymphomatous cells as subpopulations of the T and B cell systems, particularly in terms of their behavioral characteristics. This growing sophistication will make necessary the development of referral centers for the characterization of lymphoma cells, such as we have developed for the Los Angeles area in the Southern California Lymphoma Group. Initially these centers will be devoted to investigation, and only later, as therapy is based on specific cytologic distinctions, will they contribute to precise characterization and clinical diagnoses.

Growing precision in cytologic characterization using morphologic, cytochemical, and immunologic techniques will result in greater accuracy and reproducibility in the classification of malignant lymphomas. Finally, an improved understanding of the basic biology of the malignant lymphomas as neoplasms of the immune system will lead to fundamental changes in the design of therapy.

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Clinical and Surgical (Laparotomy) Evaluation of Patients With Non-Hodgkin's Lymphomas [1]

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SUMMARY

A consecutive unselected series of 423 patients with non-Hodgkin's lymphomas was staged prospectively at the Stanford Medical Center between June 1971 and June 1976. The histopathologic classification of Rappaport was used exclusively. Staging laparotomies were performed in 197 of the patients, but another 226 patients were excluded from the staging procedure for a variety of reasons, including stage IV involvement, poor surgical risk, and diagnostic celiotomy before referral to Stanford. Gastrointestinal, splenic, bone marrow, hepatic, and mesenteric lymph node involvement was very common in these patients, whereas systemic symptoms and mediastinal sites of disease were less frequently noted. After staging laparotomy, 15 patients (8%) were downstaged to a lesser extent of involvement while 62 (31%) were upstaged, primarily from clinical stage III to pathologic stage IV. Correlations were made between clinical and pathologic staging and the sites of involvement were compared between those with nodular and those with diffuse lymphomas. The accuracy of diagnostic radiologic procedures was also assessed. Although it is valuable in sequentially determining the extent of subdiaphragmatic involvement by lymphomas, we believe that staging laparotomy should still be regarded as a research procedure which will be undertaken only as indicated in centers of clinical research.

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The clinical and pathologic staging of patients with non-Hodgkin's lymphomas is a complex and often confusing topic. Only a few series have described the prospective staging of such patients by laparotomy (1–6). Other authors have described such sequential staging procedures as needle bone marrow and liver biopsies, followed by peritoneoscopy if the two needle biopsies were normal. These investigators then performed staging laparotomies if the sequential bone marrow biopsies and percutaneous and peritoneoscopy-directed liver biopsies did not reveal involvement by lymphoma (7–10). However, only a few reports have correlated the radiologic, histopathologic, and operative findings in a large number of meticulously staged patients (2,4,6). This review makes these same correlations and expands our published series of 69 staging laparotomies in patients with non-Hodgkin's lymphomas, which described an increased incidence of mesenteric lymph node, liver, bone marrow, and gastrointestinal involvement compared to Hodgkin's disease (2).

MATERIALS AND METHODS

Between June 1971, when the present Stanford

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Medical Center lymphoma protocols were begun, and June 1976, 433 consecutive, previously untreated patients with non-Hodgkin's lymphomas were staged prospectively according to the Ann Arbor classification. In this staging system, the initial biopsy (usually of a lymph node) determines the clinical stage, and all subsequent histopathologic material from bone marrow and liver biopsies and staging laparotomies is used to produce a final pathologic stage. All patients were evaluated with routine blood and platelet counts, 12-panel chemistries, and multiple radiologic examinations, including chest roentgenograms and lymphography. Most of the patients had excretory urography and, when indicated, also had full lung tomograms and barium gastrointestinal studies as previously described (2). All patients had either Westerman-Jensen or, since 1972, Jamshidi needle bone marrow biopsies. Staging laparotomy was then performed unless the initial evaluation showed such relative contraindications as bone marrow involvement, other stage IV sites of disease, advanced or very young age, or specific concurrent medical contraindications.

Five patients who had a staging laparotomy performed were excluded from this evaluation. One had Waldenström's macroglobulinemia, while two had lymphomas which could not be classified histologically. In the other two, biopsies of head and neck lesions could not distinguish lymphoma from poorly differentiated carcinoma. Five other patients were also excluded because they had unclassified malignancies, epithelial tumors originally interpreted as lymphoma before referral, or mycosis fungoides. This left 423 patients for inclusion in the final analysis.

The histopathologic classification of Rappaport was used exclusively in this series (11). In this scheme, the non-Hodgkin's lymphomas are separated into either nodular or diffuse groups and further subdivided according to cell type (lymphocytic, histiocytic, or mixed) and degree of cellular differentiation. Two of us (R. Warnke and R. F. Dorfman) reviewed the histopathologic specimens of all patients who had staging laparotomy.

Staging laparotomy was performed as previously described (2). Initially, we performed single-needle and wedge liver biopsies, but beginning 1 year ago, wedges were taken routinely from both the right and left hepatic lobes. The needle liver biopsy was then discontinued because of its low yield. An effort was made to sample the para-aortic lymph nodes which were most abnormal on lymphography. Randomly sampled mesenteric lymph nodes were also taken in most of the patients and a splenectomy was performed. An open iliac crest bone marrow specimen was also obtained. If indicated, the ovaries were moved to the pelvic midline in premenopausal women (oophoropexy) (12). Most patients with biopsy-proven bone marrow involvement did not have staging laparotomy. Initially, however, 15 patients with bone marrow involvement did have staging laparotomies, either to assess the degree of subdiaphragmatic involvement in this group or to remove the spleen in the few patients who had massive splenomegaly and/or hypersplenism.

RESULTS

All Patients (Total, 423)

Histopathology, age, and sex ratio.—Table 1 shows the distribution of patients according to the histopathologic classification of Rappaport. Forty-eight percent (206) of the 423 patients had nodular lymphomas, while 52% (217) had diffuse histologies. The most common subclassifications were nodular lymphocytic poorly differentiated (NLPD), 30%, and diffuse histiocytic (DH), 29%. No nodular lymphocytic well-differentiated or nodular undifferentiated lymphomas were encountered. The mean age for all patients was 44 years, compared to 50.8 years for the 226 patients who did not have the surgical staging procedure. The age distribution for all patients is shown in figure 1. There were 248 men (59%) and 175 women (41%). Only 17% of the patients had systemic symptoms, consisting of significant fevers, night sweats, or weight loss > 10% in the 6 months before diagnosis.

TABLE 1.—Distribution of 423 non-Hodgkin's lymphoma patients according to the Rappaport classification

	No. of patients (%)
Nodular*	
NH	23 (5)
NM	55 (13)
NLPD	128 (30)
Total	206 (48)
Diffuse†	
DH	121 (29)
DM	18 (4)
DLPD	55 (13)
DLWD	12 (3)
DU	11 (3)
Total	217 (52)

*NH = histiocytic; NM = mixed histiocytic lymphocytic; NLPD = lymphocytic poorly differentiated.

†DH = histiocytic; DM = mixed histiocytic lymphocytic; DLPD = lymphocytic poorly differentiated; DLWD = lymphocytic well differentiated; DU = undifferentiated.

Clinical and pathologic staging.—Table 2 lists the clinical and pathologic stages of the 217 patients with diffuse and 206 patients with nodular lymphomas. In both subgroups the most marked changes after the completion of evaluation were from clinical stage III to pathologic stage IV. Only 2% (four patients) in the nodular group and 5% (11 patients) in the diffuse category were downstaged to a lesser degree of involvement. Figures 2–5 depict the pathologic stages of all patients with nodular and diffuse lymphomas and those with the most frequent subtypes, NLPD and DH. Almost 50% of the patients with nodular lymphomas (102 of 206) had stage IV involvement (fig 2), another 29% had stage III, and only 21% of the patients had more limited stage I or II involvement. The most frequent pathologic stages in those patients with diffuse lymphomas were stage II (32%) and stage IV (40%) (fig 3).

TABLE 2.—Clinical vs pathologic stages in diffuse and nodular histologies (note the shift in both categories from clinical stage III to pathologic stage IV; only 15 of 423 patients were downstaged)

Clinical stage	Pathologic stage				Total
	I	II	III	IV	
		All diffuse: 217 patients			
I	32	2			34
II	1	60	2	5	68
III	2	7	24	35	68
IV	—	1	—	46	47
Total	35	70	26	86	217
		All nodular: 206 patients			
I	13	1	2	3	19
II	3	26	10	5	44
III	1	0	48	91	140
IV	0	0	0	3	3
Total	17	27	60	102	206

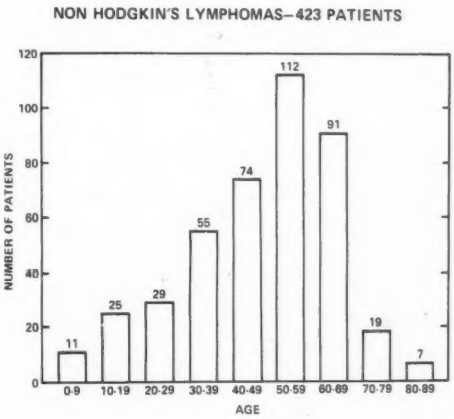

FIGURE 1.—Age distribution of all patients.

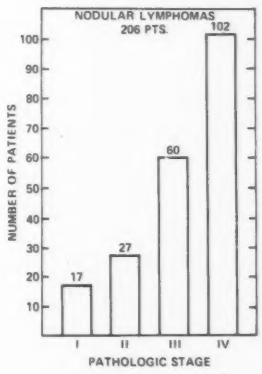

FIGURE 2.—Pathologic stage of all patients with nodular lymphomas; 80% of the 206 patients were in stages III and IV.

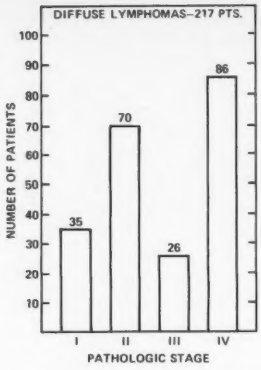

FIGURE 3.—Pathologic stage of all patients with diffuse lymphomas; pathologic stages II and IV were most frequent.

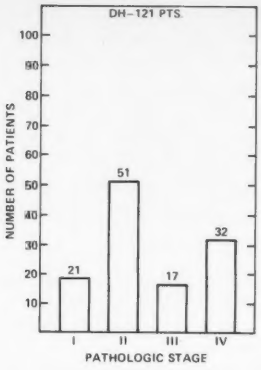

FIGURE 5.—DH—pathologic stages in 121 patients; stage II was most frequent.

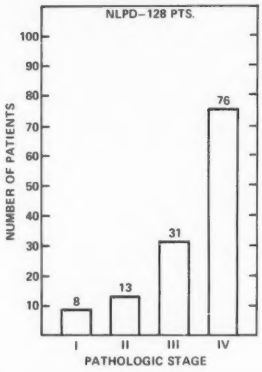

FIGURE 4.—NLPD—pathologic stages in 128 patients; 60% had stage IV involvement at the completion of evaluation.

Hepatic, bone marrow, and extranodal sites of involvement.—Lymphoma involved extranodal sites in 132 of the 423 patients (31%) (fig 6). Gastrointestinal, cutaneous, and cardiopulmonary tissues were most frequently affected. Bone marrow and liver were involved in 137 (32%) and 33 (8%) of the patients, respectively.

Radiologic findings: chest radiographs and excretory urography.—Chest radiographs showed a mediastinal mass in 108 (25%) of the 423 patients. The mediastinum was involved in 48 of 206 patients with nodular and 60 of 217 with diffuse lymphomas. Pulmonary parenchymal lesions were seen in only eight patients with nodular lymphomas, but were present in 17 of those with diffuse histologies. Full lung tomograms were performed in 162 patients, of which 15 provided information that was not available from the routine posteroanterior and lateral chest radiographs. However, this additional information gained from full lung tomography only rarely resulted in changes of stage or extent of treatment. Two hundred and seventy-five patients had excretory urograms. Ureteral obstruction was noted in only 11 patients, six with diffuse (2%) and five with nodular lymphomas (2%). All instances of ureteral obstruction, including three non-functioning kidneys, were encountered in the 226 patients who did not have staging laparotomy. Ten of the 11 patients had pathologic stage IV lymphomas and all had abdominal masses and/or ascites.

No Staging Laparotomy (226 Patients)

Characteristics of the group.—Two hundred and twenty-six of the 423 patients were excluded from staging laparotomy for such reasons as bone marrow involvement (97 patients), other stage IV sites (21), advanced or very young age (33), diagnostic laparotomies done before referral (36), medical contraindications to elective surgery (19), emergency therapy (11), previous or co-existent carcinoma (five), or refusal of staging surgery (four) (fig 7).

Classification and age distribution.—The histopathologic distribution of those patients who did not have staging laparotomy (table 3) shows that 98 (43%) patients had nodular and 128 (57%) had diffuse lymphomas. The patients who did not have laparotomy had a higher percentage of diffuse lym-

TABLE 3.—Histopathologic classification (Rappaport) of non-laparotomy group of 226 non-Hodgkin's lymphoma patients*

	No. of patients (%)
Nodular	
NH	9 (4)
NM	19 (8)
NLPD	70 (31)
Total	98 (43)
Diffuse	
DH	62 (28)
DM	11 (5)
DLPD	34 (15)
DLWD	11 (5)
DU	10 (4)
Total	128 (57)

*See table 1 for explanation of abbreviations.

phomas since almost 33% had clinical stage IV involvement at presentation. NLPD and DH were again the most common histologic subtypes. Figure 8 compares age distribution in the laparotomy and non-laparotomy groups. The latter was an older patient population, probably because age and related medical conditions contraindicated laparotomy.

Extranodal sites and liver biopsies.—Table 4 lists the extranodal sites involved in 96 (42%) of these patients. Twenty-nine (13%) of the 226 patients had percutaneous liver biopsies. Six of these procedures revealed hepatic involvement by lymphoma in a single patient in each of the diffuse subcategories and in another with NLPD.

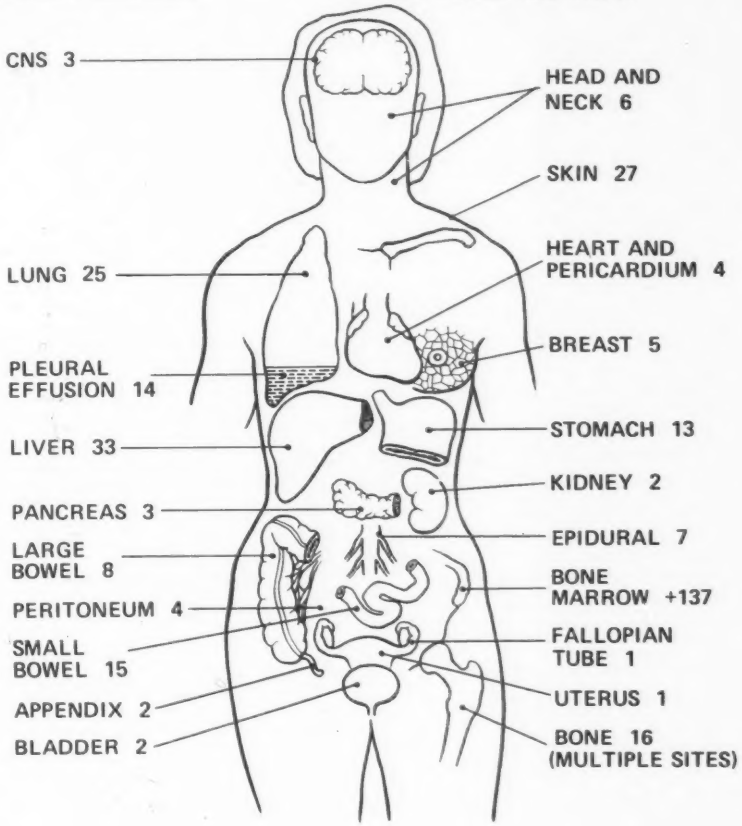

FIGURE 6.—Extranodal sites of involvement at presentation, noted in 132 (31%) of the 423 patients; 102 (47%) of 217 patients with diffuse lymphomas had extranodal involvement, as did 29 (14%) of 206 with nodular histologies. Also listed is the frequency of hepatic and bone marrow involvement.

TABLE 4.—Extranodal sites of involvement in 226 patients at presentation—non-laparotomy group

Sites of involvement	Nodular: 98 patients	Diffuse: 128 patients
Gastrointestinal-abdominal		
Small bowel	4	11
Stomach		10
Large bowel		8
Appendix		1
Pancreas		2
Peritoneal nodules	1	
Ascites (+)		2
Cardiothoracic		
Lung	5	9
Pleural effusion (+)	3	7
Pericardium		1
Heart		1
Bone	3	11
CNS-spinal cord		
Epidural		4
CNS		3
Genitourinary, gynecologic, breast		
Biadder		2
Kidney		2
Testicle		1
Breast	1	4
Fallopian tube		1
Uterus	1	
Skin	7	10
Head and neck		
Thyroid		3
Other	1	2
Total No. of patients with extranodal involvement (%)	20(20)	76(59)

Mediastinal and lung involvement.—Sixty-five of the 226 (29%) patients had mediastinal masses, 29 of the 98 with nodular and 26 of the 128 with diffuse lymphomas. Five (6%) of those patients with nodular and nine (8%) of those with diffuse lymphomas had pulmonary involvement by lymphoma. Fifty-nine (26%) of the 226 patients had full lung tomograms, and this procedure yielded additional information in six instances.

Staging Laparotomy (197 Patients)

Histopathology.—As indicated in figure 7, 226 of the 423 patients did not have staging laparotomy. Table 5 categorizes the staging laparotomy group of 197 patients by the Rappaport classification. One hundred and eight (54%) of the 197 patients had nodular and 89 (46%) had diffuse lymphomas. Multiple histopathologic diagnoses were made in 21 (11%) of the patients. Fifteen had two different histologic types of lymphoma in noncontiguous anatomic sites, while six others had "composite" lymphomas. This diagnosis of a composite lymphoma is made when two histopathologic subtypes are present in the same lymph node or within a single site. If only those patients with subdiaphragmatic involvement by lymphoma are considered (positive laparotomies), six (20%) of 32 with diffuse lymphomas and 15 (20%) of 73 with nodular histologies had multiple histologic subtypes of lymphoma in the excised specimens.

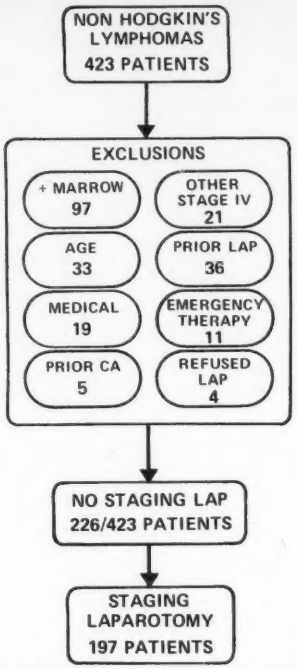

FIGURE 7.—Exclusions from staging laparotomy (226 of 423 patients).

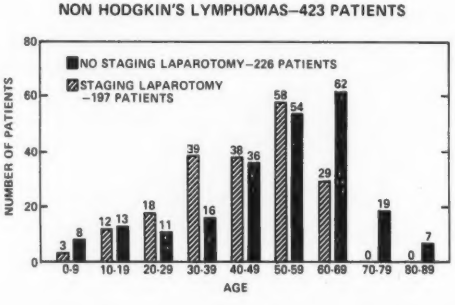

FIGURE 8.—Age distribution by decades, laparotomy (cross-hatched bars), and non-laparotomy groups (solid black bars).

TABLE 5.—Histopathologic classification (Rappaport) of 197 non-Hodgkin's lymphoma patients who had staging laparotomy*

	No. of patients (%)
Nodular	
NH	14 (7)
NM	36 (18)
NLPD	58 (29)
Total	108 (54)
Diffuse	
DH	59 (30)
DM	7 (4)
DLPD	21 (11)
DLWD	1 (0.5)
DU	1 (0.5)
Total	89 (46)

*See table 1 for explanation of abbreviations.

TABLE 6.—Postoperative complications in 197 patients (complications occurred in < 5% of the last 130 consecutive laparotomies [*see* text])

Postoperative complication	No. of patients
Left upper quadrant, abdomen	
Pancreatitis	3 (1 death)
Subphrenic abscesses	2
Gastric perforation	1
Gastric hemorrhage	1
Pulmonary	
Pneumonia	4
Empyema	1
Cardiovascular	
Arrhythmia	1
Pulmonary embolus	1
Phlebothrombosis	1
Urinary tract infections	3
Acute parotitis	1
Septicemia	1
Partial wound dehiscence	1
Wound infection	1
Total (%)	22 (11)

Complications.—Postoperative complications occurred in 22 (11%) of the 197 patients (table 6). The most common complications involved the pulmonary system or were related to the removal of massively enlarged spleens, after which pancreatitis, subphrenic abscesses, and gastric complications often occurred. There was one death in this series, in a patient who developed postoperative pancreatitis, gastrointestinal bleeding, renal failure, and enterocutaneous fistulae. The complication rate was reduced to 5% in the last 100 consecutive patients after the operative hazards associated with massive left upper quadrant abdominal involvement were recognized.

Clinical versus pathologic stage.—Table 7 compares clinical and pathologic stages in the 108 patients with nodular and the 89 with diffuse lymphomas who had staging laparotomy. Approximately 80% of the patients with nodular lymphomas were found to have pathologic stage III and IV involvement (82 of 108), whereas about one third of those with diffuse lymphomas had advanced, pathologic stage III or IV disease. Fifteen (8%) of the 197 patients were downstaged to a lesser extent of involvement, while 62 (31%) were upstaged, primarily from clinical stage III to pathologic stage IV.

Mediastinal and lung involvement.—Mediastinal involvement was found in 43 of the 197 patients

TABLE 7.—Clinical vs pathologic stages of 197 patients, laparotomy series (note shifts from clinical stage III to pathologic stage IV in both nodular and diffuse groups)*

Clinical stage	Pathologic stage				Total
	I	II	III	IV	
			Nodular: 108 patients		
I	8	1	2	3	14
II	3	13	9	2	27
III	1		37	27	65
IV	—	—	—	2	2
Total	12	14	48	34	108
			Diffuse: 89 patients		
I	17	2			19
II	1	28	2	1	32
III	2	7	10	13	32
IV	—	1	—	5	6
Total	20	38	12	19	89

*Of 197 patients, 15 (8%) were downstaged and 62 (31%) were upstaged.

(22%). Full lung tomograms were performed in 103 patients (52%) and gave information not obtained by routine chest radiographs in eight of these patients. However, this additional information did not result in a change of stage in these eight patients. Eleven patients (5%) had pulmonary involvement—three of 108 with nodular and eight of 89 with diffuse lymphomas.

Extranodal sites and bone marrow involvement.—Table 8 lists the extranodal and stage IV sites of involvement in the 197 patients who had staging laparotomy. Extranodal involvement at presentation was most frequent in patients with diffuse lymphomas (30% of the group). The areas most commonly affected were gastrointestinal, cardiothoracic, and cutaneous. One hundred and sixty-one patients had needle bone marrow biopsies that were considered to be both adequate specimens and benign. Eighteen of these patients had lymphoma diagnosed in subsequent open iliac crest marrow biopsies, an 11% incidence of false negative needle biopsies. Fifteen patients with positive needle bone marrow biopsies had staging laparotomies. Eleven had hepatic involvement and ten had enlarged spleens weighing > 400 g. Three of these patients with positive prelaparotomy bone marrow biopsies had postoperative complications. Of the remaining 21 patients, the needle marrow biopsies were inadequate in eight and no prelaparotomy marrow sample was taken in five. The other eight had needle marrow biopsies but open specimens were not obtained; all were benign.

Subdiaphragmatic Disease Sites

Spleen.—Splenectomy was performed in 192 of 197 patients (fig 9). One patient had had an earlier splenectomy, unrelated to the diagnosis of lymphoma. In two other patients the organ could not be removed with safety, and in the last two (both children) grossly normal spleens were left in place at laparotomy. All patients with spleen weights > 900 g had concomitant liver involvement. Moreover, 12 of the 18 patients whose spleens weighed > 400 g had co-existing hepatic lymphoma. Only one of the 24 palpable spleens was normal, but approximately one third of the nonpalpable spleens were involved by lymphoma. Overall, 78 (40%) of the 192 resected spleens contained lymphoma. Splenic involvement was also noted in 23 of the 28 patients with nodular lymphomas who had positive bone marrow biopsies (83%) and in eight (77%) of 11 patients with diffuse histologies and bone marrow involvement (table 9).

Liver.—This organ was involved by lymphoma in 27 (14%) of the 197 patients. Six of the 27 had only a single hepatic wedge biopsy. Another 20 patients had both hepatic wedge and needle biopsies, but in nine (45%) of these only the wedge specimen was positive. Both needle and wedge biopsies contained lymphoma in the other 11 patients. During the last 12 months, we have performed biopsies of both the right and left hepatic lobes in 27 consecutive patients, but only one had lymphoma in both wedges. We did not encounter a single case of hepatic

TABLE 8.—Extranodal sites of involvement in 197 patients who had staging laparotomies

Sites of involvement	Nodular: 108 patients	Diffuse: 89 patients
Gastrointestinal-abdominal		
Small bowel		4
Stomach		3
Appendix		1
Pancreas		1
Peritoneal nodules	3	
Cardiothoracic		
Lung	3	8
Pleural effusion (+)	1	3
Pericardium		2
Bone	1	1
CNS-spinal cord		
Epidural	2	1
Skin	2	8
Head and neck	1	
Total No. of patients with extranodal involvement (%)	9(8)	27(30)

TABLE 9.—Correlations between splenic, concomitant bone marrow, hepatic, and subdiaphragmatic lymph node involvement

	No. of patients (%) with splenic involvement and involvement of—*				
	Bone marrow	Liver	Mesenteric nodes	Splenic hilar nodes	Para-aortic nodes
Nodular	23/28(82)	16/16	39/53(74)	25/26(96)	42/67(62)
Diffuse	8/11(73)	8/8	9/17(53)	8/13(61)	13/20(65)

*Denominator = total patients with bone marrow, hepatic, or lymph node involvement.

involvement by lymphoma without concomitant splenic involvement.

Lymph nodes.—Table 10 compares the incidence of subdiaphragmatic organ and lymph node involvement in patients with nodular and diffuse lymphomas. Mesenteric lymph nodes were involved by lymphoma in 72 of the 140 patients (51%) in whom such nodes were biopsied. Splenic hilar lymph nodes were biopsied in only 75 patients, but 40 of these (53%) contained lymphoma. In general, positive findings were more common in patients with nodular (table 10) than in those with diffuse lymphomas. Table 11 shows the frequency of subdiaphragmatic organ-lymph node involvement in the most common Rappaport histopathologic subtypes, DH, diffuse lymphocytic poorly differentiated, NLPD, and nodular mixed histiocytic lymphocytic. Patients with NLPD had the highest incidence of subdiaphragmatic involvement; those with DH lymphomas had the lowest.

Lymphography.—This procedure was performed before staging laparotomy in 194 of the 197 patients. Two patients did not have lymphangiograms, while a third had this procedure performed after the staging laparotomy. Table 12 depicts the accuracy of the procedure; excluded are ten patients in whom incorrect para-aortic lymph nodes were sampled and another 14 from whom no para-aortic lymph node tissue was obtained. Interpretation was accurate in 87% of the cases when the lymphograms showed para-aortic lymph node involvement by lymphoma (true positive). The accuracy rate after para-aortic lymph node biopsies in patients with normal lymphograms was also high, 88%. Tables 13 and 14 correlate subdiaphragmatic organ and lymph node involvement by histopathologic subtype and the lymphographic findings. The frequency of spleen, liver, bone marrow, and lymph node involvement was high in patients with positive lymphograms and either nodular or diffuse lymphomas. Of the patients with nodular histologies and normal lymphograms (table 13), > 40% were found to have unsuspected splenic and mesenteric lymph node involvement. However, in those with diffuse lymphomas and a negative lymphogram, subdiaphragmatic involvement by lymphoma was rare, occurring in < 10% (table 14).

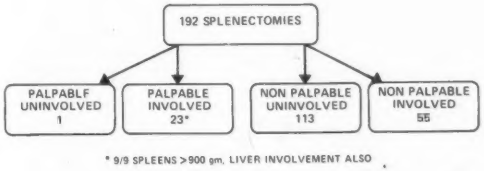
192 SPLENECTOMIES
PALPABLE UNINVOLVED 1
PALPABLE INVOLVED 23*
NON PALPABLE UNINVOLVED 113
NON PALPABLE INVOLVED 55
* 9/9 SPLEENS >900 gm, LIVER INVOLVEMENT ALSO

FIGURE 9.—Splenic findings; 5 patients did not have splenectomy (*see* Results section).

CONTIGUITY

Table 15 presents an analysis of the contiguity of lymphatic involvement in 144 patients with pathologic stage I, II, and III lymphomas who had staging laparotomy. Contiguous involvement was scored when direct lymphatic connections existed between the lymph node areas being analyzed (13). Contiguous lymphatic involvement ranged from a low of 57% in patients with Waldeyer's involvement to almost 100% in those with para-aortic and cervical adenopathy.

In patients with nodular lymphomas, supraclavicular lymph node involvement was associated with

TABLE 10.—Comparison of subdiaphragmatic organ, bone marrow, and lymph node involvement in 197 patients with nodular and diffuse non-Hodgkin's lymphomas

Site	No. of patients (%)	
	Nodular: 108 patients	Diffuse: 89 patients
Spleen	60/107(56)	18/85(21)
Liver	17/108(16)	10/89(11)
Bone marrow	29/108(27)	11/89(12)
Nodes		
Para-aortic	68/100(68)	20/80(25)
Mesenteric	55/77(71)	17/63(27)
Splenic hilar	27/44(61)	13/31(42)

TABLE 11.—Comparison of subdiaphragmatic organ, bone marrow, and lymph node findings in the 4 most common histopathologic subtypes

Subtype	No. of patients	No. of patients (%) with involvement in—				
		Bone marrow	Liver	Spleen	Mesenteric nodes*	Para-aortic nodes
DH	59	5 (8)	4 (7)	10 (17)	12/45 (27)	11 (17)
DLPD	21	2 (10)	4 (19)	4 (19)	5/14 (36)	6 (29)
NLPD	58	20 (34)	15 (26)	35 (60)	34/43 (79)	40 (69)
NM	36	7 (19)	1 (3)	17 (47)	15/23 (65)	17 (47)

*No. of patients with mesenteric node involvement/total No. with lymphoma evaluated.

TABLE 12.—Lymphographic accuracy (3 of the 197 [total] patients did not have lymphangiography [*see* Results section])

Lymphogram*	Para-aortic node biopsy		Accuracy	No. excluded from analysis because—		Total lymphograms taken
	+	–		Wrong node biopsied	No biopsy done	
+	78	12	78/90(87%)	10	11	111
–	10	70	70/80(88%)	0	3	83
						194

* + = positive; – = negative.

TABLE 13.—Correlation of subdiaphragmatic and bone marrow findings in patients with nodular lymphomas and positive or negative lymphograms

Involvement	Total patients with involvement	No. of patients (%) with involvement/ No. evaluated	
		+ lymphograms (total, 76)	– lymphograms (total, 32)
Spleen	60	47/75(63)	13/32(41)
Bone marrow	29	24/76(32)	5/32(16)
Liver	17	16/76(21)	1/32(3)
Mesenteric nodes	55	46/58(79)	9/19(47)

TABLE 14.—Correlation of subdiaphragmatic and bone marrow findings in patients with diffuse lymphomas and positive or negative lymphograms

Involvement	Total patients with involvement	No. of patients (%) with involvement/ No. evaluated	
		+ lymphograms (total, 35)	– lymphograms (total, 51)
Spleen	17	12/33(36)	5/50(10)
Bone marrow	11	8/35(23)	3/51(6)
Liver	9	7/35(20)	2/51(4)
Mesenteric nodes	17	14/27(52)	3/32(9)

TABLE 15.—Contiguity of lymphatic involvement at presentation in 144 patients with stage I, II, and III lymphomas who had staging laparotomies; 53 patients with pathologic stage IV involvement are excluded

Involved site	No. of patients				
	Total No. involved	Only site involved	Additional sites	Non-contiguous	Contiguous (%)
Right cervical	46	2	44	3	41(93)
Right supraclavicular	37	—	37	2	35(95)
Left cervical	55	9	46	6	40(87)
Left supraclavicular	49	1	48	6	42(88)
Waldeyer's	10	3	7	3	4(57)
Right axilla	29	—	29	12	17(59)
Left axilla	29	—	29	7	22(76)
Mediastinum	24	1	23	1	22(96)
Spleen	42	—	42	5	37(88)
Para-aortic	50	—	50	1	49(98)
Mesenteric	41	—	41	4	37(90)
Splenic hilar	13	—	13	1	12(92)
Iliac-inguinal femoral	59	10	49	4	45(92)
Extranodal	22	7	15	1	14(93)

subdiaphragmatic lymphoma 100% of the time when bilateral nodes were clinically positive and in over three fourths of the patients when only the right or the left supraclavicular lymph nodes were clinically positive.

In patients with diffuse lymphomas, 81% of those with bilateral supraclavicular lymph node involvement also had at least one site of subdiaphragmatic involvement; none of the five patients with right supraclavicular adenopathy had subdiaphragmatic organ or node involvement, while 42% of those with clinically involved left supraclavicular lymph nodes had subdiaphragmatic involvement.

DISCUSSION

Although it can be performed in < 50% of patients who initially present with non-Hodgkin's lymphomas (if those with stage IV disease and other contraindications are excluded from laparotomy), staging laparotomy has permitted a better understanding of the natural history and patterns of presentation and spread of these neoplasms. The high incidence of positive mesenteric lymph nodes demonstrated by staging laparotomies (72 of the 140 biopsies or 51% in this series) has made it apparent that standard inverted-Y radiation fields do not constitute adequate abdominal treatment for non-Hodgkin's lymphomas. Wider abdominal radiation portals are necessary to include the mesenteric lymph nodes in their entirety (14).

Our earlier hope that a negative lymphogram would reliably predict an absence of disease below the diaphragm has not proved to be entirely accurate, at least in patients with nodular lymphomas. Lymphoma was found in almost 50% of the resected spleens and mesenteric lymph nodes from patients with nodular lymphomas who had normal lymphograms. Therefore, a negative lymphogram does not accurately predict a low frequency of subdiaphragmatic involvement in patients with nodular lymphomas. In addition, a very high frequency of mesenteric lymph node involvement (79%) was noted when the lymphogram demonstrated positive para-aortic lymph nodes in patients with nodular lymphomas.

In patients with diffuse lymphomas and positive lymphograms, the incidence of subdiaphragmatic hepatic and mesenteric lymph node involvement ranged from 20% to 50%. However, 51 patients with diffuse histologies and normal lymphograms had a low incidence of subdiaphragmatic organ and lymph node involvement, 4%–10%. It may be possible to omit staging laparotomy in this one group if both the lymphogram and a needle bone marrow biopsy are normal. It is doubtful that peritoneoscopy will add useful information in patients with normal lymphograms and either nodular or diffuse lymphomas, since only three of 82 such patients (4%) were found to have hepatic involvement at laparotomy.

Stage IV involvement was common in the 423 patients evaluated in our medical center between 1971 and 1976. Almost 50% of those with nodular lymphomas had pathologic stage IV involvement, while 79% were included in pathologic stages III and IV. Less than 5% (five of 103) of those with diffuse lymphomas progressed from clinical stages I and II to pathologic stage IV. In those patients with nodular histologies, however, eight of 63 patients (12%) shifted to pathologic stage IV. In addition, very few patients were downstaged to a

lesser extent of disease following the various staging procedures.

Our findings show that, in contrast to Hodgkin's disease, there is an increased incidence of gastrointestinal, mesenteric, hepatic, and pulmonary involvement in patients with non-Hodgkin's lymphomas. The frequency of splenic involvement, however, is approximately equal, while fewer patients with non-Hodgkin's lymphomas had either systemic symptoms or mediastinal masses.

If patients are to be treated solely with chemotherapy or whole-body irradiation, staging laparotomy may not be important in their management. Certainly, the yield from both laparotomy and peritoneoscopy is low in patients with diffuse lymphomas and a normal lymphogram. However, it is appropriate to do staging laparotomies in clinical research centers, not only to obtain a better understanding of the natural history and patterns of spread of these lymphomas, but also to aid in treatment decisions for the individual patient. Furthermore, knowledge gained from staging laparotomies concerning the extent of mesenteric lymph node involvement has led to the introduction of newer methods of treatment such as wide field abdominal radiation techniques.

It has been suggested that splenectomy may prevent future bone marrow and/or hepatic infiltration by lymphoma in patients with initially normal spleens. In our laparotomy series it was apparent that liver infiltration was not seen without splenic involvement and that approximately 80% of patients with positive bone marrows also had involved spleens (table 5). Marrow and/or liver involvement may follow splenic infiltration in most patients with non-Hodgkin's lymphomas although this speculation remains to be proved.

The operative specimens of at least 20% of patients with positive laparotomies contained multiple histopathologic subtypes of lymphoma. Major changes in therapy occurred in half of these patients because of the presence in many of diffuse lymphomas in laparotomy specimens after initial biopsies had shown a nodular pattern. In other patients, an initial diagnosis of Hodgkin's disease was made, but nodular lymphomas were found in the operative specimens. Carefully performed laparotomies may be of great value in assessing the relative frequency and clinicopathologic settings of multiple histopathologic lymphoma subtypes.

In conclusion, we believe that the staging surgical procedure has considerable value and should be continued in medical centers that specialize in the care of patients with lymphomas and conduct clinical trials.

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Sequential Staging in Non-Hodgkin's Lymphoma [1]

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SUMMARY

The results of staging in 170 patients with non-Hodgkin's lymphoma have been reviewed; all patients were subjected to a series of sequential procedures, including lymphangiography, bone marrow biopsy, and liver biopsy (performed percutaneously, by peritoneoscopy, or by laparotomy). A high incidence of involvement of bone marrow, liver, and abdominal nodes was found in patients with nodular types of lymphoma and in those with diffuse lymphocytic lymphoma, with ≤ 20% remaining in stage I or II at the completion of staging in each of these subgroups. Only in patients with histiocytic lymphoma was there an appreciable percentage (31%) remaining in the stage I–II categories after staging. In this study, 75 patients remained in stage III or less after completing the non-surgical phase of staging, and laparotomy was utilized in only 50 patients (30%). At laparotomy, involvement of the liver or the mesenteric or portal lymph nodes was found in 81% of patients with a positive lymphangiogram but in only 18% of those with a negative lymphangiogram.

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Advances in the treatment of the non-Hodgkin's lymphomas in the past decade, including demonstration of the curability of advanced histiocytic lymphoma with combination chemotherapy (1), have encouraged efforts to develop methods for accurate pretreatment staging and posttreatment evaluation of response. New techniques for staging are now widely utilized, such as bilateral bone marrow biopsy (2), peritoneoscopy (3), and staging laparotomy (4), and the clinician is faced with multiple alternative approaches in his attempts to define the extent of disease spread. From 1971 to 1974, we undertook a prospective study of the yield of common staging techniques applied in a defined sequence in order to determine whether the use of more aggressive procedures could be curtailed by first employing more limited and less morbid procedures. The results of this study of 170 consecutive patients with non-Hodgkin's lymphoma have been reported elsewhere (5). The primary conclusion was that the high incidence of bone marrow and liver involvement in patients with nodular lymphoma and in patients with diffuse poorly differentiated lymphocytic lymphoma would make laparotomy unnecessary in the majority of patients with these histologies. In the present paper we will review these data and will devote particular attention to the relative yield of staging procedures in patients with primary sites of presentation in extranodal tissues as compared to patients with primary nodal disease.

MATERIALS AND METHODS

Patient Population and Staging Procedures

Between January 1, 1971, and September 1, 1974,

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a total of 170 consecutive patients were admitted to the Medicine Branch or Radiation Oncology Branch of the Clinical Oncology Program, DCT, NCI, with the histologically confirmed diagnosis of non-Hodgkin's lymphoma. The histologic classification scheme of Rappaport (6) was used for all diagnoses, and all pathologic material was reviewed by the staff of the Laboratory of Pathology of the Division of Cancer Biology and Diagnosis, NCI.

Following routine physical examination, blood chemistries, urinalysis, and chest roentgenograms, all patients were subjected to a routine sequence of staging studies. In the consecutive series of 170 patients skeletal films were obtained in 93%, technetium^{-99} diphosphonate bone scans in 87%, and bipedal lymphangiograms in 80%. Bone marrow biopsy of the posterior superior iliac spine was attempted in all patients, and material adequate for evaluation was obtained in 165. Liver biopsy was undertaken in 133 patients including those who were stage III or less at presentation and those who were stage IV by virtue of bone marrow involvement. Of the 104 patients with negative percutaneous liver biopsy, 91 were subjected to peritoneoscopy with multiple (four to six) liver biopsies obtained under direct vision. As a final procedure, staging laparotomy with splenectomy and wedge liver biopsy was performed in 50 patients who remained stage III or less after the more limited procedures; 25 patients in whom laparotomy was indicated according to this protocol did not undergo the procedure because of medical contraindications (13 patients) or for unspecified reasons (12 patients).

RESULTS

The pathologic characteristics of the tumors in the consecutive series of 170 patients are shown in table 1. The largest groups of patients were the nodular poorly differentiated lymphocytic (29%) and the diffuse histiocytic (24%). In this series the primary site of tumor presentation was the lymph nodes in 135 patients and was thought to be extranodal in 35 patients (20%), the most frequent extranodal sites being bone (eight patients), gastrointestinal tract (six patients), or skin (six patients).

TABLE 1.—Distribution of histologic subtypes: 170 consecutive patients, 1971–1974

Nodular	No. of patients	Diffuse	No. of patients
Lymphocytic, poorly differentiated	49	Lymphocytic, well-differentiated	6
		Lymphocytic, poorly differentiated	29
Mixed lymphocytic-histiocytic	25		
		Mixed lymphocytic-histiocytic	7
Histiocytic	7		
		Histiocytic	40
		Pleomorphic (undifferentiated or stem cell)	7
Total	81		89

Radiologic procedures (table 2) were of considerable value in delineating the extent of nodal disease. The lymphangiogram was positive in 90% of patients with nodular types of lymphoma but in only 66% of patients with diffuse types of disease, and the lowest degree of positivity was found in patients with diffuse histiocytic lymphoma (57%). In contrast, routine chest films provided evidence of hilar or mediastinal disease in only 15% of patients, and parenchymal lesions were observed in only 3%. Pleural effusions believed secondary to tumor were seen in 8% of patients. Bone scans were highly useful in detecting metastatic lesions; they were positive in 19 patients with nodal primary disease, including five patients with diffuse histiocytic lymphoma. However, confirmation of bone scan abnormalities was obtained in only four patients, three

TABLE 2.—Yield of roentgenograms in staging non-Hodgkin's lymphoma

	Chest roentgenogram				
	Negative	Mediastinal or hilar nodes	Effusion	Parenchymal lesion + effusion	Lymphangiogram (No. positive/No. tested)
Nodular	57	19	7	2	62/69 (90%)
Diffuse					
Histiocytic	29	7	4	3	21/37 (57%)
Other histologies	40	5	2	0	24/31 (78%)
Total	126 (74%)	31 (18%)*	13 (8%)	5 (3%)	107/137 (78%)

*Includes 3 patients with parenchymal lesions and 2 patients with effusion.

by skeletal roentgenograms and one by biopsy of the indicated lesion. In most instances the existence of stage IV disease in bone marrow or liver obviated the need for biopsy confirmation of metastases detected by bone scan findings.

Bone marrow biopsy yielded a high percentage of positive findings, particularly in patients with nodular lymphoma and diffuse lymphocytic subcategories where the rate of positive biopsies varied from 40% to 54% (table 3). A noticeably lower percentage of positives (15%) was found in patients with diffuse histiocytic lymphoma. The yield was slightly higher in patients having bilateral biopsies as opposed to those having only one biopsy (40% vs 34%); in 89 of 100 patients having bilateral biopsies, the biopsy findings were in agreement (both positive or both negative), while 11 patients had one positive and one negative biopsy. Assuming that the positive biopsy would have been obtained on the second attempt in half of these 11 patients, a small additional yield of approximately 5% could be expected as the result of obtaining a second bone marrow biopsy, a figure in agreement with previously published work (5).

Table 4 presents a comparison of the results of liver biopsy by three different approaches used in sequence. The yield of the three approaches was approximately equal, although it should be noted that only those patients having prior negative percutaneous biopsies had peritoneoscopy, and laparotomy was utilized only in patients having negative liver biopsies by the non-surgical techniques. Thus the additional yield of peritoneoscopy and laparotomy may represent more "occult" cases of liver involvement. In addition to the 21% yield of liver biopsy at laparotomy, two patients were found to have ascites positive for malignant cells and 14 patients had lymphoma involving porta hepatis or mesenteric lymph nodes outside usual nodal irradiation ports.

An important correlation was noted between the results of liver biopsy and lymphangiography. Of the 60 patients in this series having a positive liver biopsy, 57 had a positive lymphangiogram and in two additional patients the lymphangiogram was equivocal. Of the 26 patients with a negative lymphangiogram who underwent liver biopsy in this series by any of the three routes, only one had a

TABLE 3.—Results of bone marrow biopsy in patients with non-Hodgkin's lymphoma

	Bilateral biopsies				Unilateral biopsy	All patients	
	Both negative	1 negative, 1 positive	Both positive	Total positive/ No. of patients	Total positive/No. of patients	No. positive/ No. of patients	%
Nodular							
Poorly differentiated	17	4	12	16/33	3/15	19/48	40
Mixed	7	3	5	8/15	3/9	11/24	46
Histiocytic	5	0	1	1/6	0/1	1/7	14
Diffuse							
Well differentiated	0	0	2	2/2	4/4	6/6	100
Poorly differentiated	9	1	5	6/15	9/13	15/28	54
Mixed	3	0	1	1/4	1/2	2/6	33
Histiocytic	19	3	3	6/25	0/14	6/39	15
Stem cell	—	—	—	0/0	4/7	4/7	57
Total	60	11	29	40/100	24/65 (40%)	64/165 (34%)	39

TABLE 4.—Liver biopsy in non-Hodgkin's lymphoma

	Biopsy route					
	Percutaneous		Peritoneoscopy		Laparotomy	
	No. positive/ No. tested	%	No. positive/ No. tested	%	No. positive/ No. tested	%
Nodular	18/72	25	16/51	32	8/29	27
Diffuse						
Histiocytic	2/33	6	3/26	12	0/11	0
Other histologies	8/26	31	7/14	50	1/4	25
Total	28/131	21	26/91	29	9/44	21

positive result. As might be expected, a strong correlation was found between lymphangiogram findings and the results of liver and lymph node biopsy at laparotomy. Disease outside conventional nodal radiation fields was found at laparotomy in 22 of 28 patients with a positive lymphangiogram but in only three of 15 patients with a negative lymphangiogram. Thus the involvement of abdominal para-aortic or iliac lymph nodes appears to be an accurate predictor of disease in liver or hepatic/mesenteric lymph nodes.

The change in stage as the result of diagnostic staging procedures is shown in table 5 for the major pathologic subtypes. It is apparent that the nodular lymphomas were rarely localized to a single site or a single region. A higher percentage of patients with diffuse poorly differentiated lymphocytic lymphoma had stage I or II disease (21%), although the great majority (79%) had visceral involvement. Only among patients with histiocytic lymphoma did staging result in a distribution of patients into all four stages, 31% having local or regional disease at the completion of workup. As will be discussed in another report in this issue, the majority of these patients with stage I or II histiocytic lymphoma had disease arising in lymph nodes as opposed to extranodal sites (7).

DISCUSSION

This study has clearly shown that most patients with non-Hodgkin's lymphoma, with the exception of those with diffuse histiocytic lymphoma, have widely disseminated disease at the time of diagnosis, although differences in the patterns of organ involvement were appreciated in the various pathologic subcategories of disease. The nodular lymphomas and diffuse poorly differentiated lymphocytic lymphomas exhibited similar patterns of organ involvement, having a high incidence of positivity of abdominal lymph nodes, bone marrow, and liver. Fewer than 10% of patients with nodular lymphoma and 21% of patients with diffuse poorly differentiated lymphocytic lymphoma had stage I or II disease after exhaustive staging. In contrast, patients with diffuse histiocytic lymphoma had a significantly lower incidence of involvement of liver, bone marrow, and abdominal lymph nodes, and approximately one third were classified as stage I or II at the conclusion of workup.

These findings place in serious question the routine use of staging laparotomy in the pretreatment evaluation of patients with non-Hodgkin's lymphoma. In the majority of patients with nodular types of disease, percutaneous biopsies or peritoneoscopy yielded evidence of disseminated disease. In addition, the strong correlation of para-aortic lymph node involvement with the presence of disease outside the traditional nodal irradiation ports suggests that the decision to employ systemic therapy in patients with nodular lymphoma may be logically based on finding a positive lymphangiogram, and additional morbidity of laparotomy in this setting does not appear justified. In patients with positive lymphangiography, the less morbid percutaneous biopsy procedures have value as a baseline for judging the completeness of response to therapy. Only in patients with clinical stage I or II disease is laparotomy of obvious value by excluding the presence of occult dissemination and thus allowing local or regional radiotherapy with curative intent. It should be noted that this group composed < 10% of patients with nodular types of pathology in the current series, and the yield of laparotomy in patients with stage I–II disease was

TABLE 5.—Change in patient stage during workup: influence of pathologic subtype

		% of patients with stage—			
		I	II	III	IV
Nodular					
Poorly differentiated lymphocytic	On referral	10	18	61	10
	Final	4	0	27	69
Mixed lymphocytic-histiocytic	On referral	12	28	48	12
	Final	0	8	24	68
Diffuse					
Poorly differentiated lymphocytic	On referral	17	21	17	45
	Final	7	14	0	79
Histiocytic	On referral	13	30	30	28
	Final	8	23	25	45

markedly lower than the results in patients with stage III disease.

The present study, together with recent observations on the limited capacity of nodal radiotherapy to cure patients with stage III disease (8), leads to the conclusion that the distinction between stage III and stage IV may no longer be useful in the clinical classification of lymphomas. The traditional Ann Arbor classification is likewise difficult to apply to patients with massive intra-abdominal disease, a frequent presentation in patients with histiocytic lymphoma; in this type of presentation, the prognosis appears to be unrelated to the presence of disease above the diaphragm, but rather seems to be a function of the ability to eradicate the intra-abdominal tumor. It would appear that a simplified two- or three-stage scheme might be most appropriate for patients with non-Hodgkin's lymphomas; thus stage III might include all patients with nodal disease above and below the diaphragm, massive disease of intra-abdominal origin, or nodal primary disease and visceral involvement (currently classified as stage IV).

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Comparison of Nodal Primary Versus Extranodal Primary Histiocytic Lymphoma [1]

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Unlike Hodgkin's disease, non-Hodgkin's lymphomas frequently present with a primary site of involvement in a tissue other than lymph node. In 16%–21% of all patients with non-Hodgkin's lymphoma, the disease appears to arise in an extranodal site (1,2). The most common extranodal sites of involvement include bone, skin, gastrointestinal tract, and upper respiratory tract. Although most reviews on the presentation and staging of the non-Hodgkin's lymphomas were published before the widespread use of the Rappaport classification, recent investigations (2,3) have indicated that most extranodal primary lymphomas have a diffuse histology (83%) and the majority of these are diffuse histiocytic lymphoma.

In a recent review of malignant lymphomas (4), Aisenberg noted that "the poor prognosis of nodal non-Hodgkin's lymphomas contrasts with favorable prognosis seen in non-Hodgkin's lymphoma of many extranodal sites." Five-year survival rates after local surgery or radiotherapy have been reported as high as 50% for primary gastric lymphomas (5) and as high as 58% for primary bone lymphomas (6). This substantial cure rate with local treatment implies that in at least half of patients with primary extranodal non-Hodgkin's lymphoma, the disease was confined to the local site of presentation at the time of initial evaluation. This limited spread of disease in patients with extranodal primaries contrasts with the finding of stage I or II disease in only 14% of a recent series of 170 patients with non-Hodgkin's lymphoma subjected to extensive staging (2) and suggests that extranodal primary tumors represent a more limited form of lymphoma. An alternative explanation is that the encouraging survival statistics in the past may have been the result of the exclusion of patients with disseminated disease from these studies. The present study was undertaken to determine whether patients with diffuse histiocytic lymphoma arising in extranodal sites (gastrointestinal tract, skin, and bone) have a lower incidence of para-aortic node, liver, and bone marrow involvement than patients with nodal primary disease.

METHODS

Between January 1, 1971, and September 1, 1974, 170 consecutive patients with non-Hodgkin's lymphoma were staged at the NCI as described by Chabner et al in this issue (7). From these 170 patients, all cases of diffuse histiocytic lymphoma with primary site of presentation in lymph node, skin, gastrointestinal tract, or bone were selected for review for purposes of this study. The primary site of presentation was defined as that site in which the tumor was first noted and which was the predominant site of clinically detectable disease at the time of presentation. Biopsy confirmation of diffuse histiocytic lymphoma at the primary site of involvement was required to qualify for inclusion in this study. The records of 16 additional patients with diffuse histiocytic lymphoma presenting with extranodal sites of primary involvement were reviewed in order to provide a clearer understanding of the patterns of disease spread in patients with this type of presentation; these patients represented all additional patients with diffuse histiocytic pathology presenting with primary lesions in bone or gastrointestinal tract seen at the NCI during the period from September 1, 1974, to September 1, 1976.

The histologic classification scheme of Rappaport (6) was used for all diagnoses, and all pathologic material was reviewed by the staff of the Laboratory of Pathology of the NCI.

RESULTS AND DISCUSSION

From September 1, 1971, to September 1, 1974, 26 patients with nodal primary diffuse histiocytic lymphoma were staged at the NCI. Over a slightly longer period, September 1, 1971, to September 1, 1976, 27 patients with diffuse histiocytic lymphoma arising in an extranodal site (bone, seven; skin, three; and gastrointestinal tract, 17) were evaluated

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TABLE 1.—Diffuse histiocytic lymphoma: staging of patients with extranodal primary presentation and comparison with nodal primary patients

Site	No. of patients	No. of patients (%) Lymphangiogram	Bone marrow biopsy	Liver biopsy	Final stage IV
Extranodal					
Bone	7	4/6*	2/7	0/5	6/7
Gastrointestinal tract	17	11/15	2/17	2/17	14/17
Skin	3	2/3	0/3	1/3	2/3
Total	27	17/25 (68)	4/27 (15)	3/27 (12)	22/27† (81)
Nodal histiocytics	26	15/26 (58)	5/26 (19)	4/24 (17)	7/26† (27)

*Patients with positive lymphangiogram or biopsies/total patients tested.
†$P < 0.05$.

at the NCI. The results of staging of these 53 patients are shown in table 1. The incidence of positivity of lymphangiogram, bone marrow biopsy, and liver biopsy was essentially the same for patients with nodal primary disease as for patients with extranodal primary lymphoma. A significantly greater number of patients with primary extranodal disease were ultimately classified as stage IV, but this difference reflected the obligatory presence of visceral disease in the primary extranodal site. Thus, aside from involvement of the primary extranodal site, patients referred to the NCI with primary extranodal lymphoma arising in bone, skin, or gastrointestinal tract had an incidence of involvement of abdominal nodes, bone marrow, and liver similar to that of patients with diffuse histiocytic lymphoma arising in lymph nodes.

These results suggest that the excellent survival figures reported for extranodal primary lymphoma may be due to the exclusion of those patients with disseminated disease rather than reflecting a different pattern of tumor behavior and spread in patients with extranodal primary disease. Dissemination beyond the site of the primary lesion and draining lymph nodes was identified in 81% of patients with diffuse histiocytic lymphoma arising in extranodal tissues, a finding which emphasizes the need for careful staging before the use of local therapy with curative intent.

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Role of Staging in Childhood Non-Hodgkin's Lymphoma [1]

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SUMMARY

Childhood non-Hodgkin's lymphoma is characterized by a high incidence of leukemic transformation. A retrospective analysis of this incidence in 227 children is provided. In an attempt to identify factors associated with this phenomenon, the extent of disease in 30 recently diagnosed patients was determined by means of a modified Ann Arbor staging system. Concurrently, the staging system was utilized for the delivery of a new treatment program: chemotherapy was administered to all patients, and those with stage I and II disease also received radiation therapy to sites of bulk tumor. An overall disease-free survival of 75% was achieved. No patient with stage I disease converted to acute leukemia. The data suggest that the major utility of staging is the delineation of anatomic sites of bulk tumor. The chemotherapeutic program utilized in these patients is outlined.

[Cancer Treat Rep 61:1001–1007, 1977]

Progress in the treatment of cancer requires an understanding of the natural history of the disease. This information is essential for formulating a rational plan for diagnostic evaluation and therapy. Such considerations apply particularly to the non-Hodgkin's lymphomas in childhood where, because of changing concepts, considerable confusion has developed regarding the utility of clinical and histologic classification. This confusion has been compounded by attempts to combine data and results relating to children with those of adults despite known differences in the natural history and epidemiologic features.

Non-Hodgkin's lymphoma in children is characterized by a high incidence of leukemic transformation. The rate varies from 15% to 70% in most published series (1–11). This has led to attempts to treat the disease with antileukemic regimens, with encouraging results. However, radiation therapy and/or surgery have also produced cures in children with clinically limited disease (4,12). Staging to assess the extent of disease, therefore, is important. Adequate staging could aid in providing:

1. better understanding of the natural history and biologic behavior of the tumor;
2. assessment of the feasibility of disease extirpation by surgery;
3. indications for the delivery of radiation therapy;
4. identification of patients with systemic disease to be treated principally with chemotherapy;
5. estimate of prognosis; and
6. intercomparison of results between institutions using the same staging system.

The importance of staging as a guideline to therapy has been clearly and convincingly demonstrated in Hodgkin's lymphoma where the tumor appears to spread by contiguity (13). In contrast, diffuse non-Hodgkin's lymphoma in childhood is characterized by *early* widespread dissemination occurring in a far less predictable fashion. Because of this pattern of spread and the tendency to leukemic transformation, some investigators have questioned the role of staging in childhood non-Hodgkin's lymphoma.

To determine the potential utility of staging and possibly identify factors associated with leukemic transformation, we reviewed the records of 227 children with non-Hodgkin's lymphoma who were admitted to the Sidney Farber Cancer Institute and Children's Hospital Medical Center from 1947

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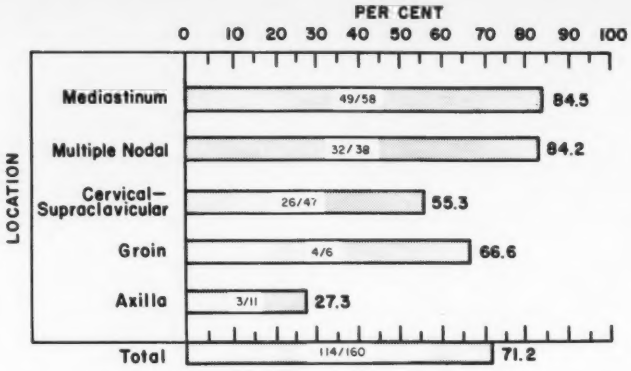

FIGURE 1.—Non-Hodgkin's lymphoma in children, 1947–1972: conversion to leukemia (nodal).

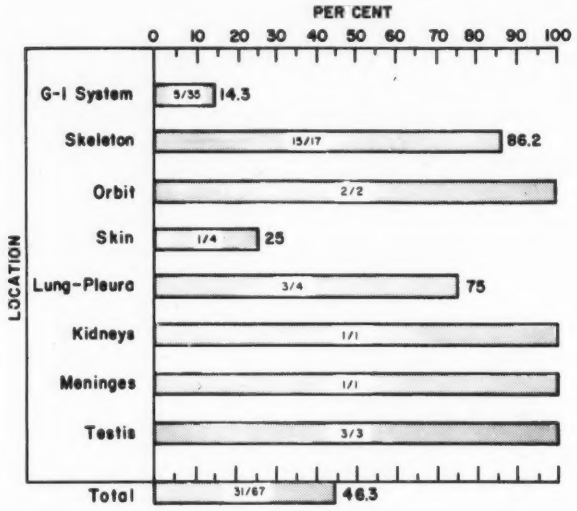

FIGURE 2.—Non-Hodgkin's lymphoma in children, 1947–1972: conversion to leukemia (extranodal).

to 1972. The analysis was simplified by grouping all histologic subtypes together although it was recognized that several disease entities were involved. Leukemic transformation in these patients was defined as the appearance of blast cells in the peripheral blood rather than in the bone marrow and consequently represents an underestimate if compared to criteria defined by others (1,13). The results, outlined in figures 1 and 2, confirm the strong tendency for leukemic transformation in childhood non-Hodgkin's lymphoma, particularly in patients with mediastinal and diffuse nodal involvement (8–11).

The foregoing study also confirmed that a number of children with limited disease were cured with excisional biopsy and/or radiation therapy, as has been demonstrated in several other centers. For example, in the Stanford experience, treating with radiation therapy after rigorous staging achieved permanent control of non-Hodgkin's lymphoma in 55% of children with stage I disease—45% of the patients had recurrence outside the radiation field

(4). In stage II and III disease, long-term control was achieved in 40% of patients treated with appropriate extended-field radiation therapy. No patient with stage IV disease achieved control.

The above data provide justification for adopting a staging system, particularly if localized potentially radiocurable disease can be identified. In addition, because leukemic transformation is a distinct possibility, it appears appropriate to do an extensive evaluation to determine possible factors associated with this phenomenon and identify patients at high risk.

In an attempt to develop a prognostic staging system for childhood non-Hodgkin's lymphoma, several groups have used systems other than the Ann Arbor classification (14–17). Sequential reports sometimes demonstrate that such staging systems have undergone considerable change (11,17). Others have used the Ann Arbor system, recognizing its limitations (4,18).

An ideal staging system for diagnostic evaluation in childhood non-Hodgkin's lymphoma has not been developed. In 1973, we elected to adopt the Ann Arbor system for staging Hodgkin's disease. The classification is identical to that originally described except for laparotomy (13). From considerations of natural history discussed above, the patient was assumed to have pre-existing microscopic dissemination, and chemotherapy was administered. In view of this, we concluded that surgical intervention (other than initial biopsies) for the purpose of staging was excessive and we therefore used only noninvasive techniques. Since tumor which was locally confined was potentially curable with radiation therapy, an attempt was made to identify such areas. In contrast to our previous practice, invasion of the bone marrow (blast count $> 5\%$) was now defined as leukemic transformation.

This paper will review the utility of the staging system in 30 consecutive patients and demonstrate its application to treatment. It will also present an outline of the histologic subtypes.

DIAGNOSTIC EVALUATIONS

Routine histories and physical examinations were obtained. In some cases where diagnosis was uncertain, specific inquiry was made regarding the ingestion of drugs or trauma from a cat which may cause cat-scratch fever and mimic childhood non-Hodgkin's lymphoma. Laboratory studies included a cbc count, liver function tests, BUN and serum electrolytes, creatinine, and uric acid determinations. Particular attention was given to the presence of an elevated serum LDH level which could be indicative of disseminated disease (19).

Initial evaluations comprised radiographic examination of the chest, bone marrow aspiration and biopsy, and lumbar puncture. Marrow biopsies were obtained in addition to aspirates in view of reports demonstrating superiority of the former over the latter (20,21). The bone marrow studies were repeated at 9-week intervals and lumbar puncture studies were repeated during "prophylactic" treatment for meningeal leukemia and at 18-week intervals thereafter.

The following ancillary investigations were obtained as indicated: barium studies of the gastrointestinal tract, iv pyelography, bipedal abdominal lymphangiography, technetium 99_m liver and spleen scans, radioisotope bone scans, and skeletal survey.

TREATMENT

Concurrently with the introduction of the Ann Arbor staging system, a new treatment protocol for non-Hodgkin's lymphoma was initiated based on a recently developed leukemia protocol (22,23). Full details are outlined in figure 3. In patients with localized stage I and II disease, an attempt was also made to exploit the utility of radiation therapy by administering, with a 4- or 8-Mev accelerator, total doses of 3000–4000 rads to bulk tumor in appropriate fields. The central nervous system was treated "prophylactically" with intrathecal methotrexate[1] and cranial irradiation (2400 rads). The latter was omitted in children who had had irradiation to the head and neck as part of their primary therapy.

RESULTS

Thirty patients were entered in the study, 17 boys and 13 girls. Their ages ranged from 4 to 19 years (median, 12 years). The primary lesions were located in the abdomen in seven patients, mediastinum in ten patients, bone in five patients, and in the neck, tonsil, paraspinous area, axilla, or brain in the remaining eight patients.

The investigations yielded the following results (table 1). One patient had parenchymal involvement of the lungs and eight patients had pleural effusions. Thoracentesis in the latter revealed malignant cells. Barium studies of the gastrointestinal tract did not reveal any abnormalities. Abdominal non-Hodgkin's lymphoma was detected by laparotomy in seven patients after symptoms of obstruction or perforation or the discovery of abdominal masses on clinical examination.

[1]Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-.

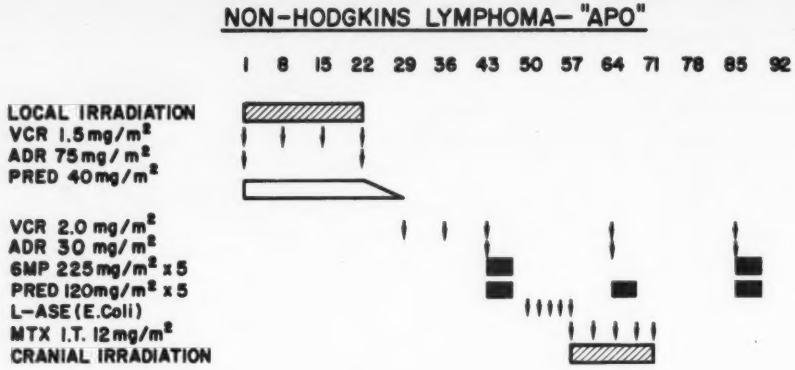

FIGURE 3.—Local irradiation to primary sites was administered concurrently with vincristine (VCR), adriamycin (ADR), and prednisone (PRED) to patients with stage I and II disease. ADR was omitted when radiation therapy was given to the gastrointestinal tract or to the oropharynx. 56,000 IU of L-asparaginase (L-ASE) was given to children < 6 yrs and 28,000 IU to children > 6 yrs on alternate days for 5 injections. Intrathecal methotrexate (MTX I.T.) was administered twice weekly for 5 injections during cranial irradiation. 75% of the dose of ADR was administered during cranial irradiation, and 6-mercaptopurine (6MP) was omitted because of possible myelosuppression. The total cumulative dose of ADR was 450 mg/m²; this was replaced by MTX, 7.5 mg/m², administered daily for 5 days every 3 wks concurrently with VCR, 6MP, and PRED.

Bipedal abdominal lymphangiography was performed in seven patients. Three of these patients presented with apparent localized tonsillar disease in the head and neck, three had disseminated disease, and one had positive inguinal nodes. There were no positive findings. For technical reasons, the procedure was not performed in patients < 6 years.

Iv pyelography, a rapid, non-invasive procedure, was performed on 20 patients in an attempt to demonstrate enlargement of retroperitoneal nodes. Results were positive in two patients, one with regional spread from pelvic bone lymphoma and the other with disseminated disease.

Three of ten patients had positive liver-spleen scans. One had a laparotomy with negative findings. In three additional patients, the results of the liver-spleen scans were equivocal. Radioisotope bone scans were performed on 14 patients; only those with primary osseous lymphoma had positive results. Similarly, of 14 patients examined by skeletal survey, detectable lesions were seen only in those with primary lymphoma of the bone. One patient had malignant cells in the cerebrospinal fluid and, concurrently, disseminated disease involving lymph nodes, a pleural effusion, and retroperitoneal disease.

The investigations described above resulted in the following classification, with the respective number of patients: stage I, six; stage II, ten; stage III, one; and stage IV, 13. The low incidence of stage III disease conforms with that in other series of non-Hodgkin's lymphoma in children (15,18).

RESPONSE

Twenty-nine of the 30 patients achieved a complete response and 22 remain in continuous remission from 5 to 32 months. One failed to achieve a response but responded to alternate therapy and is now disease-free. One patient died of encephalopathy of an unknown cause while still in remission. Five patients converted to acute leukemia and one relapsed and died from extensive pulmonary lymphoma. Figure 4 shows the disease-free survival calculated by the life-table technique. As a basis of comparison, survival is also presented for 280 patients with non-Hodgkin's lymphoma previously treated at the Sidney Farber Cancer Institute and Children's Hospital Medical Center. The overall survival in the study group is approximately 75% and the difference is significant ($P < 0.001$). This achievement compares favorably with the results reported in the recent literature (11,14,17,18,24).

The lesions in these 30 patients, when classified histologically according to the criteria of Rappaport (25), were as follows: diffuse undifferentiated lymphoma, seven; diffuse well-differentiated lymphocytic lymphoma, one; diffuse poorly differentiated lymphocytic lymphoma, nine; mixed lymphoma, two; and histiocytic lymphoma, ten. In one patient the lesion could not be categorized.

Of six patients who relapsed and one who failed to achieve a response, four had stage II disease and three had stage IV disease. The presenting sites of tumor in the stage II patients were tonsil,

TABLE 1.—Results of staging and classification in 30 children with non-Hodgkin's lymphoma

Patient No.	Age (yrs)	Sex	Site	Disease stage	Histology*	Response status† (mos)
1	10	M	Abdomen	I	UL	CR (33)
2	8	M		I	PDLL	CR (10)
3	6	M		II	UL	Failure (1)
4	13	M		II	UL	Relapse (2)
5	6	F		II	PDLL	CR (21)
6	8	M		IV	UL	Relapse (2)
7	14	M		IV	PDLL	Relapse (16)
8	12	M	Mediastinum	II	PDLL	CR (21)
9	4	F		II	?	CR (32)
10	17	F		IV	UL	Relapse (7)
11	13	F		IV	PDLL	CR (28)
12	10	M		IV	PDLL	CR (19)
13	13	M		IV	PDLL	CR (22)
14	6	F		IV	HL	CR (18)
15	5	M		IV	HL	CR (31)
16	6	M		IV	HL	CR (21)
17	19	F		IV	HL	CR (33)
18	14	F	Axilla, para-aortic	IV	HL	CR (33)
19	14	F	Axilla, chest, pleura	IV	HL	CR (11)
20	18	F	Cervical, inguinal	III	HL	CR (28)
21	10	F	Cervical	I	UL	CR (17)
22	10	M	Cervical, tonsil	II	UL	Relapse (2)
23	9	F		II	HL	Died, encephalopathy
24	10	M	Paraspinous	II	PDLL	Relapse (5)
25	11	F	Brain	I	PDLL	CR (7)
26	10	M	Bone	I	WDLL	CR (25)
27	11	M		I	ML	CR (34)
28	12	M		II	HL	CR (13)
29	17	M		II	HL	CR (11)
30	16	F		IV	ML	CR (13)

*All patients had a diffuse pattern. UL = undifferentiated lymphocytic lymphoma; PDLL = poorly differentiated lymphocytic lymphoma; HL = histiocytic lymphoma; ML = mixed (lymphocytic-histiocytic) lymphoma; WDLL = well-differentiated lymphocytic lymphoma.

†CR = complete remission.

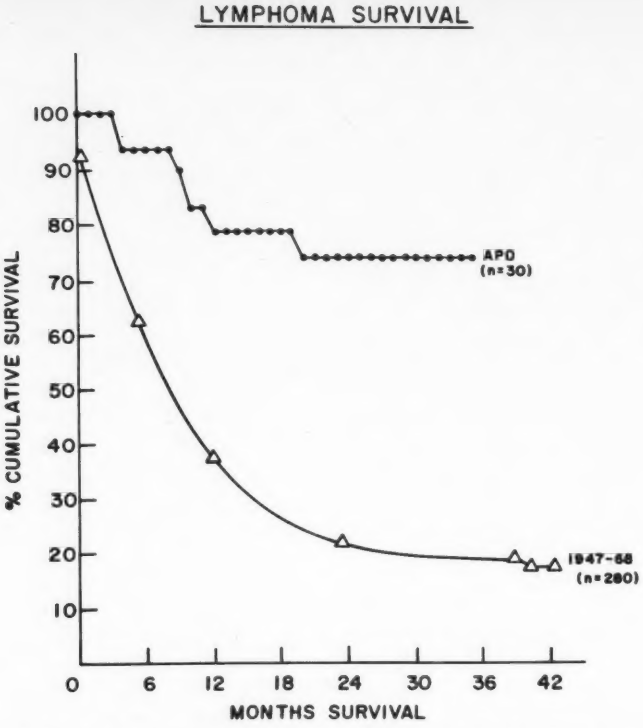

FIGURE 4.—Actuarial survival for 30 children with non-Hodgkin's lymphoma treated from 1973 to 1976 with APO (adriamycin, prednisone, and vincristine) and radiation therapy. The historical control represents 280 patients previously treated at the Sidney Farber Cancer Institute and Children's Hospital Medical Center from 1947 to 1968.

one; abdomen, two; and paraspinous area, one. The sites in the stage IV patients were abdomen, two; and mediastinum, hilum, and lung, one.

DISCUSSION

The major purpose of staging was to delineate anatomic sites of localized bulk disease. These sites were treated with radiation therapy and chemotherapy with optimum effect: no patient with stage I disease converted to acute leukemia.

Relapse occurred in patients with stage II and IV disease. In these patients, histology (undifferentiated) and site (abdomen) were apparently more predictive of relapse than was stage. All patients had either proved or presumptive B-cell disease (22). In several instances, disseminated relapse was concurrent with or preceded by local recurrence. In view of the results achieved in stage I patients, future investigation might concentrate on the delivery of more effective radiation therapy to bulk tumor in patients with more advanced disease. Accurate staging is a logical requirement for identification of these sites.

Effective chemotherapy has substantially improved the prognosis in childhood non-Hodgkin's lymphoma. Since current techniques cannot identify patients who can be cured with radiation therapy alone, chemotherapy should be administered to all children with non-Hodgkin's lymphoma. This approach recognizes the limitations of the current staging system.

In most patients, a reasonable assessment of the stage of disease was obtained by means of physical examination, chest radiograph, lumbar puncture, and bone marrow examination. Patients with abdominal primaries were diagnosed at laparotomy (performed because of obstruction, symptoms of perforation, or masses found on physical examination).

Radionucleotide studies appeared to be of limited value. Our experience also suggests that only pa-

tients with more extensive disease will show positive results with bipedal abdominal lymphangiography and iv pyelography. It is likely that histology, functional classifications, and tumor markers (26) will become the major indicators of prognosis and of chemotherapy while staging will identify the extent of disease and serve as a guide to radiation therapy and possibly surgery.

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Systematic Re-Staging in the Management of Non-Hodgkin's Lymphomas[1]

Terence S. Herman and Stephen E. Jones[2,*]

For the Southwest Oncology Group

SUMMARY

One hundred patients with advanced non-Hodgkin's lymphoma in apparent clinical remission after combination chemotherapy had systematic re-staging to assess the completeness of response. Eighteen of these patients were found to have residual disease, predominantly in lymph nodes (eight patients) and bone marrow (seven patients). Patients with persistent lymphoma more often had stage IV disease (72% vs 54%) and constitutional symptoms (44% vs 28%) than patients without detectable disease. Twenty of the 82 patients without demonstrable disease at re-staging have relapsed, with a mean time to relapse after re-staging of 4 months. Predominant sites of relapse were the lymph nodes (16 patients) and skin (four patients). The sites of disease detected at re-staging and at the time of relapse were predictable: in 80% of patients with nodular lymphoma and in 60% of those with diffuse lymphoma, disease was found in sites originally involved by lymphoma. Significantly fewer re-staging studies were performed on those patients who have relapsed than were performed on those who have remained in remission ($P < 0.05$), and in some of the relapsing patients "early relapse" appears to reflect inadequate re-staging evaluations for residual disease. All future lymphoma trials should incorporate systematic re-staging, emphasizing a thorough re-evaluation of all sites of disease determined at initial staging in order to standardize the definition of complete remission. Furthermore, such re-staging should be performed in clinical practice before treatment is stopped. The accuracy of systematic re-staging in detecting residual lymphoma may be enhanced by a more careful pretreatment evaluation for extent of disease, by individualizing re-staging procedures for particular patients, and by using new diagnostic techniques to detect occult disease.

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Treatment for patients with malignant lymphoma has improved rapidly in the last decade. Hodgkin's disease and certain types of non-Hodgkin's lymphomas are now considered potentially curable (1–3) and total eradication of the malignant cells has become a realistic goal of current treatment. However, with these advances have come new dilemmas. Whereas in the past only a few patients achieved complete resolution of clinical disease, today the signs and symptoms of lymphoma disappear in most cases. Thus, we are now faced with the need for a more rigorous definition of complete remission (CR), one which will have prognostic importance and value as an endpoint of treatment. Recently, the Southwest Oncology Group (SWOG) initiated a treatment program which incorporates a plan for systematic and thorough re-evaluation of patients for evidence of lymphoma before discontinuation of treatment. In this paper, we report our initial findings with "systematic re-staging" to assess the completeness of response to treatment.

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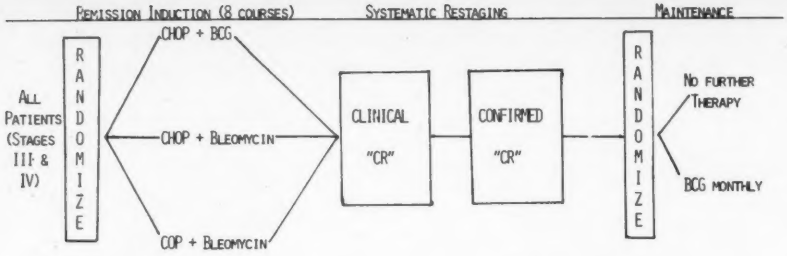

FIGURE 1.—Schema for SWOG treatment protocol 7426/7427 for patients with advanced non-Hodgkin's lymphoma. For details of treatment regimens *see* Patients and Methods section.

PATIENTS AND METHODS

In October 1974, the SWOG began a clinical trial of combination chemotherapy for non-Hodgkin's lymphomas designed to define the minimum treatment necessary to induce sustained remissions of disease (SWOG study 7426/7427). Only patients with biopsy-proven disease of an advanced extent and no prior chemotherapy are eligible. All lymphomas are classified according to the system of Rappaport (4), and the original biopsy material from each patient is submitted for additional review by the Lymphoma Pathology Panel and Central Repository (5). Patients are evaluated for extent of disease before treatment (6) and staged according to the criteria of the Ann Arbor Conference (7). They are then assigned at random to one of three chemotherapy programs intended to induce a CR. These treatments are as follows:

1. COP-bleomycin (four drugs): *cyclophosphamide*, 125 mg/m²/day given orally for 14 days starting on Day 1; *vincristine* (Oncovin), 1.4 mg/m² given iv on Days 1 and 8 (maximum of 2 mg/injection); *prednisone*, 100 mg/day given orally on Days 1–5; and *bleomycin*, 4 mg/m² given iv on Days 1 and 8. Courses are repeated every 28 days if the peripheral blood cell counts are adequate.
2. CHOP-bleomycin (five drugs): *cyclophosphamide*, 750 mg/m² given iv on Day 1; *adriamycin* (hydroxyldaunorubicin), 50 mg/m² given iv on Day 1; *vincristine*, 1.4 mg/m² given iv on Day 1 (maximum of 2 mg/injection); *prednisone*, 100 mg/day given orally on Days 1–5; and *bleomycin*, 4 mg/m² given iv on Day 1. Courses are repeated every 21 days if the blood cell counts are adequate.
3. CHOP-bacillus Calmette-Guérin (BCG) (five drugs): same regimen as in CHOP-bleomycin therapy except for substitution of high-viability Pasteur BCG for bleomycin. BCG is given by scarification at a dose of 1 ampule ($6 \pm 4 \times 10^8$ viable organisms) on Days 8 and 15 of each 21-day treatment cycle.

The basic design of this ongoing study is shown in figure 1. Remission-induction therapy for responding patients consists of eight courses of treatment given at 3–4-week intervals, followed by "systematic re-staging" (outlined in fig 2) if all clinical signs and symptoms of lymphoma have disappeared. Patients considered to be free of disease at re-staging are then assigned at random to receive either no further therapy or BCG by scarification at monthly intervals for 18 months with close followup for signs of relapse.

The records of the first 100 patients achieving an apparent CR after receiving eight courses of therapy and having systematic re-staging have now been reviewed in detail and the results of re-staging have been analyzed with regard to the clinical features of the patients, histologic type, initial sites of involvement, type of treatment, and actual number of re-staging studies done. [For this analysis, a maximum of seven studies was considered possible

1. Careful physical examination
2. Biopsy of any residual enlarged lymph nodes, particularly if region was involved initially
3. Routine laboratory tests: cbc count, liver function studies, etc
4. Chest radiography (with whole-lung tomograms if initially abnormal)
5. Bone marrow core biopsy
6. Repeat tests of other initially abnormal studies:
   a) lymphangiogram (or followup abdominal radiography if dye persists)
   b) liver-spleen scan
   c) liver biopsy
   d) tumor scans (gallium-67 citrate or indium-111 bleomycin)
   e) laparoscopy
7. Consideration of exploratory laparotomy in selected cases

FIGURE 2.—Procedures in the re-staging of patients in apparent CR.

for each patient including: (*a*) chest radiography; (*b*) bone marrow core biopsy; (*c*) liver biopsy; (*d*) liver-spleen scan; (*e*) lymphangiogram; (*f*) biopsy of specific lymph nodes; and (*g*) laparotomy.] Patterns of early relapse in the group of patients with no detectable disease at re-staging and the relationship between occurrence of relapse and thoroughness of re-staging have also been analyzed.

Although this SWOG study provides for continuation of therapy to 11 courses for patients with occult disease detected at re-staging or obvious persistent disease (clinical partial remission) after eight courses, this analysis includes neither these patients nor patients considered treatment failures. These data will be reported with the overall results of the study at a later date.

The time to relapse is calculated from the date of completion of re-staging.

RESULTS

Eighteen of the 100 patients believed to be in CR by clinical criteria were found during systematic restaging to have persistent disease. The clinical characteristics of these patients and of those patients in whom no disease was detected at re-staging are presented in table 1. There were no significant differences between these groups with respect to age, sex ratio, histologic type of lymphoma, or induction treatment. However, the patients found to have persistent disease more often had stage IV disease and constitutional symptoms initially than those with confirmed CR (72% vs 54% and 44% vs 28%, respectively).

A summary of the results of tests done at initial staging and at systematic re-staging is presented in table 2. In general, lymphography and bone marrow biopsy proved to be the most useful procedures both for initial staging and subsequent re-staging. Lymphography (or followup abdominal radiography) revealed disease in eight (11%) of 71 patients, and bone marrow biopsy detected disease in seven (8%) of 87 patients at re-staging. Chest radiography, including tomography, was the least helpful, revealing disease in only one of the 100 patients re-examined.

Radionuclide liver-spleen scans were interpreted as abnormal in three (6%) of 54 patients at re-

TABLE 1.—Clinical and pathologic features of 100 patients with non-Hodgkin's lymphoma in apparent CR before systematic re-staging (whole patient group and according to results of re-staging)

Feature	No. of patients (% of total)		
	Whole group (total: 100)	Residual disease detected during re-staging (total: 18)	No disease detected during re-staging (total: 82)
Mean age in yrs (range)	53 (19–79)	53	53
Sex (M/F)	50/50	10/8	40/42
Histologic type*			
Nodular	58	10 (55)	48 (59)
NLPD	41		
Diffuse	42	8 (45)	34 (41)
DH	29		
Pathologic stage†			
II_E	3	0	3 (4)
III	40	5 (28)	35 (43)
IV	57	13 (72)	44 (54)
Constitutional ("B") symptoms†	31	8 (44)	23 (28)
Prior radiation therapy	3§	0	3
Induction treatments‡			
COP-bleomycin	36	10 (55)	26 (32)
CHOP-bleomycin	34	3 (17)	31 (38)
CHOP-BCG	30	5 (28)	25 (30)

*System of Rappaport (ref 4); NLPD = nodular lymphocytic, poorly differentiated; DH = diffuse histiocytic.

†According to criteria of the Ann Arbor Conference on Staging (ref 7).

‡*See* description of treatment programs in Patients and Methods section.

§All had nodular lymphoma with a long interval between completion of radiation therapy and recurrence of disease and all had stage IVA disease (ie, bone marrow or skin involvement) at the start of chemotherapy.

TABLE 2.—Results of individual diagnostic procedures during initial staging and systematic re-staging in 100 patients with non-Hodgkin's lymphoma (according to histologic type)

Staging procedure	Nodular lymphoma: 58 patients		Diffuse lymphoma: 42 patients	
	Initial staging	Re-staging	Initial staging	Re-staging
	No. positive/ No. performed (%)	No. positive/ No. performed (%)	No. positive/ No. performed (%)	No. positive/ No. performed (%)
Peripheral lymph node biopsy	52/54 (96)	0/1	37/38 (97)	0/1
Chest radiography	4/58 (7)	0/58	13/42 (31)	1/42 (2)
Bone marrow biopsy	25/57 (44)	5/50 (10)	11/39 (28)	2/37 (5)
Lymphangiogram	32/48 (67)	5/41 (12)	20/29 (69)	3/30 (10)
Liver-spleen scan	10/32 (30)	1/32 (3)	9/26 (35)	2/22 (9)
Liver biopsy*	11/28 (39)	1/19 (5)	8/22 (36)	1/12 (8)
Splenectomy	14/21 (67)	0/0	8/16 (50)	2/3 (67)
Abdominal node biopsy	17/21 (81)	0/2	10/16 (63)	1/3 (33)

*Includes both percutaneous biopsies and open biopsies performed during laparotomy.

TABLE 3.—Sites of disease during systematic re-staging: correlation with known initial sites

Histologic type	Total No. of patients	No. of patients with persistent disease in—						% of sites found during re-staging	
		Abdominal lymph nodes*	Bone marrow	Liver†	Spleen	Lung	Multiple sites§	Originally involved	Originally uninvolved or involvement unknown
Nodular	10	5	5	1	0	0	1	82	18
Diffuse	8	4	2	1	2	1‡	2	60	40

*Detected by lymphangiogram (or followup abdominal radiograph if dye persisted) except in 1 case biopsied at re-staging laparotomy.
†Biopsy-proven cases only.
‡Confirmed at autopsy.
§Minimal incidence. *See* Results section for discussion.

staging, but in only one of these was lymphomatous involvement documented histologically. (This patient had splenomegaly observed with a scan and was subsequently found to have splenic involvement at laparotomy and splenectomy.)

At re-evaluation, liver biopsy revealed lymphoma in two (6%) of 31 patients. Neither patient had had liver scanning performed before biopsy. Only two patients had biopsy of residual enlarged peripheral lymph nodes; neither had histologic evidence of lymphoma.

Five patients had an exploratory laparotomy at re-staging, and persistent lymphoma was demonstrated in three. (Two of these patients had splenic involvement and the third had para-aortic nodal involvement.)

Repetition of tests with abnormal results at initial staging clearly had the greatest clinical utility in detecting lymphoma at re-staging. Continuing abnormalities indicative of lymphoma were found in eight (17%) of 46 repeat lymphangiograms, five (14%) of 36 repeat bone marrow core biopsies, three (18%) of 16 repeat liver-spleen scans, and two (13%) of 16 repeat liver biopsies. In contrast, repetition of initially normal studies appeared to have little clinical value, with the possible exception of repeat bone marrow biopsy which revealed lymphoma in two (4%) of 50 patients whose first bone marrow examinations had been normal. When liver-spleen scans (33 cases) or lymphangiograms (12 cases) were repeated after being normal at staging, not a single repeat study was abnormal.

The sites of persisting lymphoma found at re-staging are shown in table 3. Since re-staging was usually terminated when one site of lymphoma was discovered, it was not possible to determine the total number of patients who may have had persistent disease in multiple sites. However, at least three patients had multiple sites of involvement demonstrated at re-staging.

When the sites of disease found at re-staging were compared with the sites of disease at staging,

TABLE 4.—Clinical and pathologic features of patients relapsing after systematic re-staging vs those of patients remaining in remission (as of June 1976)

Feature	No. of patients (% of total)	
	Relapsing (total: 20)	Remaining in remission (total: 62)
Mean age (yrs)	56	52
Sex (M/F)	10/10	30/32
Histologic type*		
Nodular	8 (40)	38 (61)
Diffuse	12 (60)‡	24 (39)
Pathologic stage†		
II_E	0	3 (5)
III	12 (60)	19 (31)
IV	8 (40)	40 (65)
Constitutional ("B") symptoms†	7 (35)	18 (29)
Prior radiation therapy	0	3
Mean time (mos)		
To relapse	4	
Of followup		7

*System of Rappaport (ref 4).
†According to criteria of the Ann Arbor Conference on Staging (ref 7).
‡9 of the 20 relapsing patients (total) had diffuse histiocytic lymphoma.

it was found that in 82% of patients with nodular lymphoma and 60% of patients with diffuse lymphoma, lymphoma persisted in sites previously known to be involved. Seven (77%) of nine patients with abdominal lymph node involvement at re-staging had had involvement in the same anatomic area at staging. Five (71%) of seven patients with bone marrow involvement at re-staging had had bone marrow involvement initially. Although the number of cases is small, patients with diffuse lymphoma tended to have disease at re-staging in sites not previously known to be involved more frequently than did patients with nodular lymphoma.

The 82 patients considered to be in CR after re-staging have been followed for evidence of relapse. As of June 1976, 20 (24%) of these patients have had recurrence of lymphoma with a mean time to relapse of 4 months (range, 1–12 months) (calculated from the completion of re-staging). The mean time of observation for the remaining patients is 7 months. The clinical and pathologic features of the patients who have relapsed and those who have remained continuously free of disease are presented in table 4. There are no significant differences between the two groups. It is interesting to note, however, that nine (45%) of the 20 relapsing patients had diffuse histiocytic lymphoma. Thus far, early relapse has been independent of the type of initial induction treatment and of the use of BCG maintenance.

Table 5 shows the sites of relapse for the 20 patients. In almost all cases, patients relapsed in areas previously involved by lymphoma. In 13 (81%) of 16 patients with lymph node relapse, the nodal sites were those originally involved at staging. Both of the patients who relapsed in the bone marrow had had bone marrow involvement initially, and two of the four who relapsed in the skin had had skin involvement initially.

The average number of tests performed per patient during re-staging did relate to the outcome of re-staging and subsequent status. Patients thought to be free of disease at re-staging had a slightly higher number of tests than did patients who were found to have persisting disease, although this difference was not significant. When the average number of tests performed for those patients who have relapsed (3.3 per patient) was compared with the number for nonrelapsing patients (3.7 per patient), however, the difference was significant ($P < 0.05$).

DISCUSSION

This study demonstrates the importance of careful evaluation of patients for evidence of persisting

TABLE 5.—Sites of disease at relapse: correlation with sites of disease at staging

Histologic type	Total No. of patients	No. of patients relapsing in—							% of relapse occurring in—	
		Nodes	Bone marrow	Skin	Liver	Spleen	Lung	Multiple sites*	Sites of known previous involvement	Other sites†
Nodular	8	7	2	1	0	0	0	2	80	20
Diffuse	12	9	0	3	0	1	0	1	62	38

*Minimal incidence. *See* Results section for discussion.
†New or previously unevaluated sites.

lymphoma even though all signs and symptoms of the disease may have disappeared. Eighteen of 100 patients with clinical resolution of disease were found to have residual lymphoma when they had systematic re-staging (fig 2). These results have considerable implications for the definition of CR as used in current clinical trials, since they indicate that without rigorous re-staging, CR rates may be grossly overestimated.

In addition, several reports have suggested that documentation of CR is important prognostically in both Hodgkin's disease and the non-Hodgkin's lymphomas (1–3,8,9). For example, in one recent investigation of combination chemotherapy for patients with diffuse histiocytic lymphoma, six of 18 patients having re-staging were found to have residual lymphoma. Whereas the 12 patients who had no evidence of disease after careful re-staging have remained continuously free of disease (with a median duration of unmaintained remission of 12+ months), the patients with residual disease discovered at re-staging have not survived significantly longer than partial responders or even non-responders (8).

The clinical characteristics and sites of disease for the 18 patients with residual disease found at re-staging and for the 20 patients who relapsed soon after the completion of re-staging were quite similar. The sites most frequently involved were lymph nodes (especially retroperitoneal nodes), bone marrow, liver, and, in relapsing patients, the skin. In both groups the sites of persistent lymphoma at re-staging and recurrent disease at relapse closely reflected the pattern of initial involvement. Both at re-staging and at early relapse, disease was found in previously involved sites in 80% of patients with nodular lymphoma and in 60% of those with diffuse lymphoma. These similarities and the short median time from re-staging to relapse suggest that those patients who relapsed early and those with residual disease at re-staging may both represent patients with incomplete remissions. This study also suggests that in the patients who relapsed early, residual lymphoma was not detected at re-staging. This conclusion is supported by the finding that significantly fewer re-staging studies were performed in the group of patients who have relapsed as compared with those who have remained free of disease. It is probable that some of these early relapses could have been avoided by a more meticulous re-staging examination, since in several instances initially abnormal tests were not repeated.

On the basis of this analysis we believe that we can make several recommendations for improving the accuracy of re-staging.

First, a thorough pretreatment diagnostic evaluation (6,10) is essential for clear identification of all potential sites of disease, since residual disease at re-staging will be found in these locations.

Second, re-staging should be sufficiently individualized to emphasize comprehensive re-evaluation of all previously known disease sites. For example, a patient with known liver involvement might require liver-spleen scanning, percutaneous liver biopsy, laparoscopy with biopsy, or even laparotomy with open biopsy to document a CR in that particular organ (8,10). Multiple bone marrow core biopsies might be helpful, even for those patients without initial involvement (11). Repeat lymphography should be performed in patients with initial retroperitoneal lymph node involvement (12).

Third, serious consideration must be given to the use of laparoscopy (13) in selected patients and even laparotomy with splenectomy (14) in those patients in whom retroperitoneal, hepatic, or splenic disease was initially present or is suspected at re-staging. In this study, three of five laparotomies detected residual lymphoma.

Fourth, multiple skin biopsies of previously affected areas and examination of the specimens with electron microscopy might be useful in those patients with initial skin involvement by lymphoma. In this series, two of the four patients who relapsed in the skin had such involvement originally.

Fifth, although there are serious drawbacks to the use of currently available tumor-imaging agents like gallium-67 citrate and indium-111 bleomycin for defining minimal residual disease (15,16), other new imaging techniques such as computerized axial tomography show great promise (17) and it is likely that we will come to rely more heavily on these methods in the future. In addition, research in the area of tumor markers, cell sorting, and in vitro assays of tumor stem cells may provide new means of assessing the presence of minimal residual disease (18,19).

It is clear that systematic re-staging should be mandatory in all patients with non-Hodgkin's lymphoma who have achieved clinical disappearance of disease where discontinuation of therapy is being considered. Moreover, modern lymphoma treatment trials must incorporate rigorous re-staging in their design in order to derive accurate and reproducible results.

LIST OF COMPOUNDS

Adriamycin: NSC-123127; CAS reg. No. 23214-92-8
Bleomycin: NSC-125066; CAS reg. No. 11056-06-7; [2,4'-bithiazole]-4-carboxylic acid, 2'-(2-aminoethyl)-, monohydrate
CHOP = cyclophosphamide, adriamycin (hydroxyldaunorubicin), vincristine (Oncovin), and prednisone
COP = cyclophosphamide, vincristine (Oncovin), and prednisone

Cyclophosphamide: NSC-26271; CAS reg. No. 6055–19–2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate

Prednisone: NSC-10023; CAS reg. No. 53–03–2; pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-

Vincristine: NSC-67574; CAS reg. No. 2068–78–2; leurocristine, sulfate (1:1)

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Peritoneoscopy: A Technique to Evaluate Therapeutic Efficacy in Non-Hodgkin's Lymphoma Patients [1]

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SUMMARY

Peritoneoscopy was performed in 22 patients with non-Hodgkin's lymphoma as a re-staging technique to rule out relapse or persistence of active disease after intensive chemotherapy and/or radiotherapy. Fifteen patients with previous hepatic involvement achieved a complete clinical remission; however, five patients (33%) had persistent disease proved by biopsy at peritoneoscopy. In seven patients suspected to have a clinical relapse, peritoneoscopy biopsies documented relapse in three patients (43%), including two patients with negative percutaneous liver biopsies. Because of its low morbidity rate (4%), peritoneoscopy can be utilized to re-stage hepatic involvement by non-Hodgkin's lymphoma patients more accurately than percutaneous liver biopsies and with less morbidity than laparotomy.

[Cancer Treat Rep 61:1017–1022, 1977]

The widespread use of the prognostic Rappaport histologic classification and systematic staging procedures has produced a better understanding and characterization of the behavior of the non-Hodgkin's lymphomas. Chabner et al (1,2) have shown that 65% of all non-Hodgkin's lymphoma patients have stage IV disease at the completion of initial staging work-up. Often, the extranodal disease is clinically occult and is discovered only at the time of a routine systematic biopsy of organs at risk for involvement. Jones and colleagues (3) have reported that at biopsy at least 18% of patients with nodular disease have marrow involvement with lymphoma. Chabner et al (1) have confirmed this observation and demonstrated bone marrow involvement in 46% of patients with nodular lymphoma and in 32% of patients with diffuse lymphoma. Other studies have documented similar rates of marrow involvement depending on the intensity of the search (4,5).

In addition to frequent bone marrow involvement, the liver is often involved by lymphoma at initial presentation. Using a sequential biopsy approach of percutaneous liver biopsy (PLB), peritoneoscopy with multiple needle biopsies if PLB was negative, and finally laparotomy in patients who otherwise had stage I–III disease, Chabner et al (1) demonstrated that 58% of nodular lymphoma patients and 27% of those with diffuse lymphoma have hepatic involvement at the time of diagnosis.

As reported at this symposium, the Medicine Branch of the NCI has demonstrated that the ability to achieve a well-documented complete remission with combination chemotherapy is of prognostic significance not only for the diffuse lymphomas but also for the nodular lymphomas (6). These data are based on careful re-staging of patients thought to be in a complete clinical remission after induction therapy with combination chemotherapy regimens: CVP (cyclophosphamide, vincristine, and prednisone) for patients with lymphocytic lymphoma (7), C-MOPP (cyclophosphamide, vincristine [Oncovin], procarbazine, and prednisone) for patients with mixed histiocytic-lymphocytic and histiocytic lymphoma (8), or BACOP (bleomycin, adriamycin, cyclophosphamide, vincristine [Oncovin], and prednisone) for patients with diffuse histiocytic and diffuse mixed histiocytic-lymphocytic lymphoma (9). Peritoneoscopy has been used as an alternative to laparotomy to stage Hodgkin's disease at the NCI. Our original studies (10) and those of others (11,12)

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have established the utility of this approach. In addition, this procedure has been used to evaluate liver disease as part of the non-Hodgkin's lymphoma sequential staging study reported here (2), to stage and re-stage ovarian cancer, and to selectively evaluate patients with breast carcinoma and malignant melanoma.

In an attempt to evaluate the importance of achieving a documented complete remission in non-Hodgkin's lymphoma, we have used this technique routinely to initially stage patients before therapy and to re-stage those patients achieving a complete clinical remission.

MATERIALS AND METHODS

The patient receiving re-staging peritoneoscopy is admitted to the hospital the day before peritoneoscopy and has a clinical re-evaluation. Normal coagulation status is verified using a prothrombin time, a partial thromboplastin time, a thrombin time, and a platelet count. The patient is not allowed anything orally for 8 hours before the procedure. Peritoneoscopy is performed in an operating suite using local anesthesia with xylocaine after pre-medication with Demerol and Phenergan. Patients are monitored by an anesthesiologist for changes in pulse rate, blood pressure, and cardiac rhythm. The peritoneoscopy entry site is usually 1–2 cm below the umbilicus in the midline; however, when abdominal scars preclude this entry, a site is chosen along the lateral edge of either the right or left rectus muscle. A 1-cm skin incision is made and blunt dissection is carried to the fascia. A pneumoperitoneum needle is inserted while the patient tenses the abdominal wall. Using a handpump fitted with a Millipore filter,[4] a pneumoperitoneum is then created with room air. Because the risk of the procedure is increased by the presence of abdominal scars overlying adhesions, we routinely aspirate with a 22-gauge lumbar puncture needle attached to a syringe through the tract proposed for trocar insertion. In this manner, adhesions or other obstacles which will inhibit or retard free aspiration of air will be detected. If the initial site chosen for entry does not permit trocar insertion, an alternate site is prepared. Once a clear entry tract is confirmed, the trocar is inserted, and through it the peritoneoscope is introduced. Light is provided by a high-intensity external source through a fiber optic system. These studies employed a Storz peritoneoscope.[5] A single-puncture Wildhirt peritoneoscope that used an 11-mm trocar and allowed passage of biopsy instruments through a side cannula was employed routinely. These scopes permit the operator to visualize liver, spleen (if present), portions of mesentery and omentum, and occasionally porta hepatis, and multiple biopsies of the liver can be taken under direct visualization, even in patients who have had a previous laparotomy. After the removal of the peritoneoscope at the close of the procedure, the pneumoperitoneum is reduced by opening the valve in the trocar, by having the patient perform the Valsalva maneuver, and by employing direct manual pressure to the abdomen. The initial skin incision is closed with 4-0 nylon sutures.[6] The patients are kept at complete bed rest and under close observation during the immediate postoperative period. If recovery is uneventful, the patients are able to sit up for dinner and are fully ambulatory and ready for discharge the next morning. Patients having a peritoneoscopy within the past 12 months were excluded from this report because the followup period is too short to permit evaluation of the impact of peritoneoscopy upon their subsequent clinical course.

Patients Having Routine Re-Staging

Ninety-one patients had a peritoneoscopy as part of their sequential staging evaluation before the initiation of their therapy. Of these, 35 had liver involvement documented by biopsy at peritoneoscopy or subsequent laparotomy; 25 of these patients were entered into chemotherapy trials. Fifteen patients with previous liver involvement had a peritoneoscopy as part of their systematic re-staging procedure, and in the remaining ten patients, a complete clinical remission has not been achieved or the followup time is too short to confirm the validity of this re-staging procedure. All patients who had re-staging peritoneoscopy were thought to be in complete remission based upon clinical evaluation, liver function tests, roentgenograms, and repeat bone marrow aspirations (and biopsies in patients who had bone marrow involvement before therapy). PLBs were not performed in this patient population because 14 of the 15 patients who had liver involvement initially were missed during PLB. Seven patients had nodular poorly differentiated lymphocytic lymphoma (NPDL) and had been treated with CVP combination chemotherapy; four patients with nodular mixed histiocytic lymphoma (NML) had received C-MOPP combination chemotherapy; two patients with diffuse well-differentiated lymphocytic lymphoma (DWDL) and one patient with diffuse poorly differentiated lymphocytic

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[6] Davis and Geck, American Cyanamid Co, Pearl River, NY.

TABLE 1.—Results in non-Hodgkin's lymphoma patients having routine re-staging peritoneoscopy

Patient No.	Histology*	Previous pathologic disease stage (site)	Previous therapy (No. of courses)	Re-staging work-up (sites biopsied)†	Results of liver biopsy†	Complications	Subsequent course (mos)	
							Remission	Survival
1	NML	IVA (liver and bone marrow)	C-MOPP (6)	Bone marrow (WNL)	+	None	0	40+
	NML	IVA (liver and bone marrow)	C-MOPP (10)	None	–	None	36+	36+
2	NML	IVB (liver and lung)	MOPP (12) C-MOPP (6)	Previous scope (+)	–	2-unit transfusion	28+	28+
3	NML	IVA (liver and bone marrow)	C-MOPP (8)	Bone marrow (WNL)	–	None	24+	24+
4	NML	IVA (liver)	C-MOPP (6)	None	–	None	38+	38+
5	DHL	IVA (liver and skin)	C-MOPP (6)	None	–	None	46+	46+
6	DWDL	IVA (liver and bone marrow)	CVP (8)	Bone marrow (WNL)	–	None	18	53+
7	DWDL	IVA (liver and bone marrow)	CVP (12)	Bone marrow (WNL)	–	None	19	61+
8	DPDL	IVA (liver)	CVP (8)	None	+	None	0	34+
9	NPDL	IVA (liver)	CVP (6)	None	–	None	55	61+
10	NPDL	IVA (liver)	CVP (6)	None	+	None	0	44+
	NPDL	IVA (liver)	CVP (10)	Previous scope (+)	+	None	0	38+
	NPDL	IVA (liver)	CVP (14)	Previous scope (+)	+	None	?	23+
11	NPDL	IVA (liver and ascites)	CVP (10)	None	+ (ascites, +)	None	0	42+
	NPDL	IVA (liver and ascites)	CVP (14)	Previous scope (+)	– (ascites, –)	None	6	36+
12	NPDL	IVA (liver)	CVP (8)	None	–	None	28+	39+
13	NPDL	IVA (liver and bone marrow)	CVP (6)	Bone marrow (WNL)	–	None	3	25
14	NPDL	IVA (liver and bone marrow)	CVP (6)	Bone marrow (WNL)	–	None	35+	41+
15	NPDL	IVB (liver and bone marrow)	CVP (6)	Bone marrow (±)	+	None	0	30

*See Materials and Methods for definitions of histologic types.
†+ = positive; ± = equivocal; – = negative. WNL = within normal limits.

lymphoma (DPDL) were treated with CVP; and one patient with diffuse histiocytic lymphoma (DHL) was treated with C-MOPP (table 1).

Patients With Suspected Relapse

Seven patients with non-Hodgkin's lymphoma had a total of eight peritoneoscopies because of clinically suspected relapse that could not be documented by other re-staging techniques (table 2). Two patients had NML, two had NPDL, and one each had NHL, DPDL, and diffuse undifferentiated lymphoma (DUL). Five of the seven patients had been treated with combination chemotherapy and two had received radiotherapy. Indications for peritoneoscopy included one or more hepatic abnormalities in five patients (ie, hepatomegaly in four patients, elevated alkaline phosphatase and/or transaminases in three, and obstructive jaundice in one patient), non-specific constitutional symptoms in one patient, and an abnormal lymphangiogram in one. Three of seven patients had a negative repeat PLB within 1 week before peritoneoscopy. The other patients did not have a PLB because it had been negative during their initial staging evaluation before therapy.

RESULTS

Patients Having a Routine Re-Staging Peritoneoscopy

Fifteen patients had a total of 19 re-staging peritoneoscopies. Three patients had multiple procedures separated by intervals of therapy for per-

TABLE 2.—Results in non-Hodgkin's lymphoma patients having re-staging peritoneoscopy for suspected clinical relapse

Patient No.	Histology*	Previous pathologic disease stage (site)	Previous therapy (No. of courses)	Re-staging work-up‡	Results of liver biopsy‡	Complications	Subsequent course (mos)	
							Remission	Survival
1	NML	IIIA†	MOPP (6)	Upper GI series abnormal; hepatomegaly; liver function tests abnormal; PLB (–)	+	None	3	13
2	NML	IVB (liver and lung)	MOPP (6)	Liver function tests abnormal; hepatosplenomegaly	+	None	0	42+
	NML	IVB (liver and lung)	MOPP (12)	Liver function tests abnormal; hepatosplenomegaly	+	None	0	36+
3	NHL	IVA (liver)	Total body and nodal irradiation	± Liver function tests abnormal; splenomegaly; PLB (–)	±	None	3	6
4	NPDL	IVA (bone marrow)	CVP (14)	Obstructive jaundice; ± liver function tests abnormal; PLB (–)	Porta hepatis nodes (+)	None	53+	60+
5	NPDL	IVA (liver and bone marrow)	CVP (6)	± Lymphangiogram; bone marrow × 2 (WNL)	–	None	6	20+
6	DPDL	IVA (liver and bone marrow)	Hemibody and total body irradiation	Elevated erythrocyte sedimentation rate; abnormal IgM	+	None	13+	21+
7	DUL	IVA (liver)	CVP (6)	Hepatomegaly	–	None	10+	15+

*See Materials and Methods for explanation of histologic types.
†Clinical stage.
‡+ = positive; ± = equivocal; – = negative. WNL = within normal limits.

sistent residual disease (table 1). In every instance, patients had hepatic involvement before chemotherapy and achieved an apparently complete clinical remission. Seven of these patients previously had bone marrow involvement and all were re-staged with bone marrow biopsies that were either negative (six patients) or equivocal (one patient). Five of 15 patients (33%) had positive peritoneoscopies. Patient 10 (NPDL) had persistently positive liver biopsies after six, ten, and 14 cycles of CVP therapy. Patient 11 (NPDL) was positive after ten cycles of CVP, but negative after repeat peritoneoscopy after an additional four cycles of CVP. Patient 15 (NPDL) and patient 8 (DPDL) had positive peritoneoscopies documenting residual disease and never achieved a complete remission. Patient 1 (NML) received an additional four cycles of C-MOPP therapy because peritoneoscopy revealed residual hepatic involvement after six cycles of C-MOPP. A repeat peritoneoscopy after an additional four cycles was negative. Patient 8 (DPDL) had positive peritoneoscopies documenting residual disease and never achieved a complete remission. In addition, patient 2 (NML), whose initial two peritoneoscopies revealed residual disease, subsequently achieved a complete remission as documented by his third re-staging peritoneoscopy. (*Note:* patient 2 in table 1 is also patient 2 in table 2.)

Patients With Suspected Relapse

Peritoneoscopy was positive in five of eight procedures, including patient 2 (NML) whose peritoneoscopy was positive after both six and 12 cycles of MOPP (mechlorethamine, vincristine [Oncovin], prednisone, and procarbazine) (table 2). Two of the three patients with a negative PLB subsequently had positive biopsies at peritoneoscopy. Patient 3 had a "highly suspicious" peritoneoscopy after a negative PLB; this patient relapsed in the subcutaneous tissues of the thorax 3 months later. Patient 6 (DPDL) had a hepatic relapse (documented by peritoneoscopy) after radiotherapy. This patient subsequently was treated with more total body irradiation and has achieved a second clinical remission which has lasted 13+ months. Of the two patients with negative peritoneoscopies, patient 5 had a lymph node relapse 6 months later, and

patient 7 (DUL) remains in complete remission 10+ months after peritoneoscopy.

Complications

One patient having his third re-staging peritoneoscopy had evidence of postoperative hemorrhage requiring transfusion of 2 units of whole blood and in-patient observation for an additional 4 days. No other complications, either major or minor, were observed. This complication rate, 4%, is equivalent to that previously reported from this institution for approximately 300 patients with a wide range of underlying diseases (13).

DISCUSSION

Long-term survival in non-Hodgkin's lymphoma is now possible in a significant proportion of patients provided a therapeutic response can be obtained. Data presented elsewhere in this symposium demonstrate that successful remission induction carries a favorable prognosis for patients with nodular lymphoma and for those with diffuse lymphoma if the remission is verified pathologically as well as clinically (6).

One of the major problems in the management of patients with malignant disease is determining when sufficient amounts of effective therapy have been administered. Since many patients have clinically occult bone marrow and/or hepatic involvement before therapy, it must be demonstrated that these extra lymphatic sites are free of disease before a patient can be declared in remission and therapy is discontinued. Repeat bone marrow aspirates and biopsies are relatively easy to perform and adequate material for pathologic evaluation can be obtained with minimal morbidity. Re-evaluation of hepatic involvement, however, is more difficult. As has been reported (1,4,5,14), staging laparotomy in this patient population carries a significant morbidity rate. The study by Chabner et al (1) demonstrated that peritoneoscopy could identify occult hepatic disease in 28% of patients who had previously had a negative PLB. Peritoneoscopy has, therefore, been used at our institution to re-stage non-Hodgkin's lymphoma patients.

Of the seven patients clinically suspected of relapse, peritoneoscopy was positive in four (57%). All four received further therapy and have achieved a complete remission. These four have all survived longer than the median for patients with the same stage and histologic subtype who failed to achieve a complete remission (6).

Of the 15 patients thought to be in complete remission clinically, five were found to have residual occult liver disease. One NPDL patient had three consecutively positive peritoneoscopies after six, ten, and 14 cycles of CVP therapy. This patient received four more cycles of CVP and subsequently has refused further therapy; she is alive at 23+ months. A second patient (patient 2 in both tables 1 and 2) initially had been peritoneoscopied twice for suspected clinical relapse of Hodgkin's disease after six and then 12 cycles of MOPP. Because both procedures were positive, his initial biopsy material was re-evaluated and the tissue diagnosis was amended to NML. He received six cycles of C-MOPP and his third re-staging peritoneoscopy showed no evidence of residual disease. He has been in complete remission for 28+ months. After further therapy that was documented by a subsequent re-staging peritoneoscopy, two patients who initially had positive re-staging peritoneoscopies achieved a complete remission. Both have survived longer than the median for patients with the same stage and histologic subtype who failed to achieve a complete remission (6). Peritoneoscopy showed that ten patients had achieved a complete remission; all ten have survived longer than the median for patients with the same stage and histologic subtype who failed to achieve a complete remission (6). Five of these patients have subsequently relapsed, all in previous sites of nodal involvement; none have relapsed initially in the liver.

Based on our experience, we have incorporated peritoneoscopy into our routine re-staging evaluation for patients with non-Hodgkin's lymphoma who clinically appear to have achieved a complete remission. In addition, other specific indications for peritoneoscopy include the diagnostic evaluation of hepatic dysfunction or serial determination of disease status in patients whose disease cannot be followed by other methods. Specific contraindications include past or present serum hepatitis (HAA+), thrombocytopenia of $< 50{,}000$ cells/mm^3, and a prolonged prothrombin time ($> 50\%$ of control) or partial thromboplastin time ($> 50\%$ of control) unless it can be corrected by parenteral replacement of appropriate factors. Relative contraindications include previous abdominal radiotherapy, large mediastinal masses, and/or compromised pulmonary function tests.

In summary, non-Hodgkin's lymphoma patients who achieve biopsy-proved complete remissions have a better prognosis than patients who achieve partial responses. This is true not only for the diffuse lymphomas, but also for nodular lymphomas (6). Peritoneoscopy is capable of detecting residual hepatic involvement undetected by PLB, thereby allowing the physician to more accurately evaluate the effect of therapy on intrahepatic disease. With

its low morbidity rate, peritoneoscopy can be used repeatedly to assess the disease status of patients receiving therapy for non-Hodgkin's lymphoma without incurring the morbidity and mortality of laparotomy.

ADDENDUM

Subsequent pathologic review of all our patients with NML has resulted in the recent reclassification of patient 2 (originally diagnosed as Hodgkin's disease, then amended to NML); this patient is now thought to have lymphomatoid granulomatosis, a new syndrome with histologic features and clinical behavior similar to those of the nodular lymphomas (15).

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Validity of the Ann Arbor Staging Classification for the Non-Hodgkin's Lymphomas [1]

Saul A. Rosenberg [2,*]

SUMMARY

The Ann Arbor staging classification has proved to be valuable for Hodgkin's disease. When proposed in 1971 it was thought that it could also be applied to the non-Hodgkin's lymphomas. The diversity of the non-Hodgkin's groups, the continued evolution of histopathologic classifications, and the great frequency of advanced disease in the lymphocytic subgroups make the Ann Arbor classification of only limited value for the non-Hodgkin's lymphomas.

[Cancer Treat Rep 61:1023–1027, 1977]

A valid staging classification for a neoplastic disease is important for at least four reasons: (1) to provide important prognostic information for different sites and extent of the disease, (2) to assist the physician in selecting the most appropriate therapeutic program, (3) to provide a standardized system which permits comparisons of therapeutic results, and (4) to provide an accepted descriptive system which communicates the extent of the disease.

It is appropriate to examine the Ann Arbor system, currently the most widely accepted staging classification for the non-Hodgkin's lymphomas, to determine if the system meets these requirements.

The Ann Arbor Staging Classification

The staging of the lymphomas, which has been slowly evolving over the past 40 years, culminated in the agreement of a group of international experts convened at Ann Arbor, Michigan, in 1971 (1). A committee, formed to make recommendations concerning an acceptable staging classification for Hodgkin's disease, modified the previous four-stage system adopted at similar conferences in Rye, New York (2), and Paris in 1965 (3). The Ann Arbor system differed from the Rye-Paris system chiefly by defining the E subgroup, a disease setting with limited extranodal disease which had a relatively favorable prognosis. This decision was based primarily on the data of Musshoff et al (4), but also on data of others. In addition, the Ann Arbor classification acknowledged the importance of defining the surgical diagnostic procedures used to determine the extent of the disease. This additional step emphasized the important differences between the clinical stage of the disease and the pathologic stage, the latter determined by additional surgical procedures after the initial diagnostic biopsy.

The Ann Arbor system has proved to be valuable for Hodgkin's disease. Figure 1 shows the differences in survival of the four different stages defined at Ann Arbor. Moreover, the Ann Arbor stages correlate with the disease-free survivals which in time define the probability of cure. Figure 2, from the data of Kaplan (5) for Hodgkin's disease, illustrates the validity of the E-lesion concept.

One advantage proposed for the Ann Arbor staging classification was that it would be applied readily to the non-Hodgkin's lymphomas. The E lesion of the Ann Arbor system, which did not denote an unfavorable prognosis in Hodgkin's disease, allowed for this more frequent presentation of the non-Hodgkin's group. However, the Ann Arbor conference presented no data to support the prognostic value of any of the stages for the non-

[1] Some of the data reported herein were obtained from studies done in collaboration with Drs. Henry S. Kaplan and Eli Glatstein and were supported in part by Public Health Service grants CA-05838 and CA-08122 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare; the reporting of this paper was supported by grant CA-19892.

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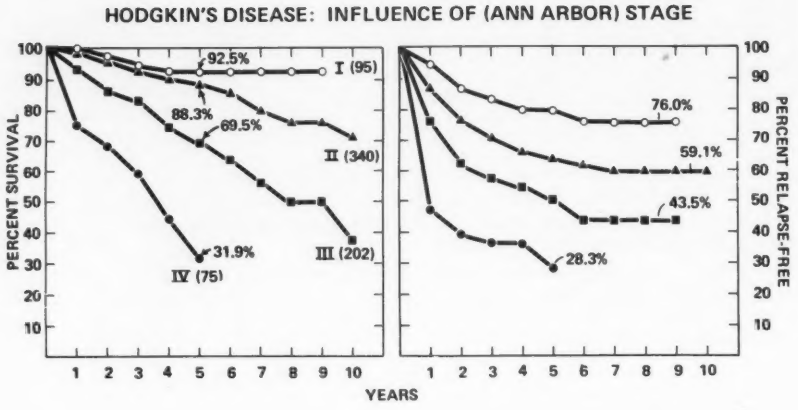

FIGURE 1.—Actuarial analysis of 713 previously untreated patients with Hodgkin's disease in relation to the Ann Arbor classification. (*From* ref 5.)

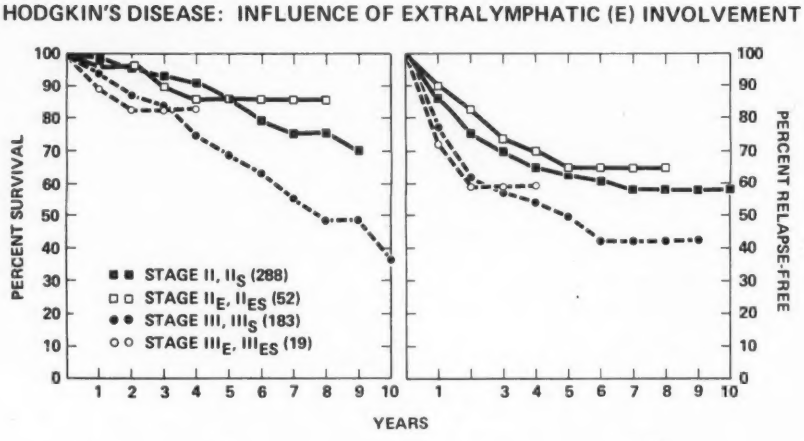

FIGURE 2.—Influence of localized extralymphatic (E) involvement within stages II and III on survival and disease-free survival for Hodgkin's disease. (*From* ref 5.)

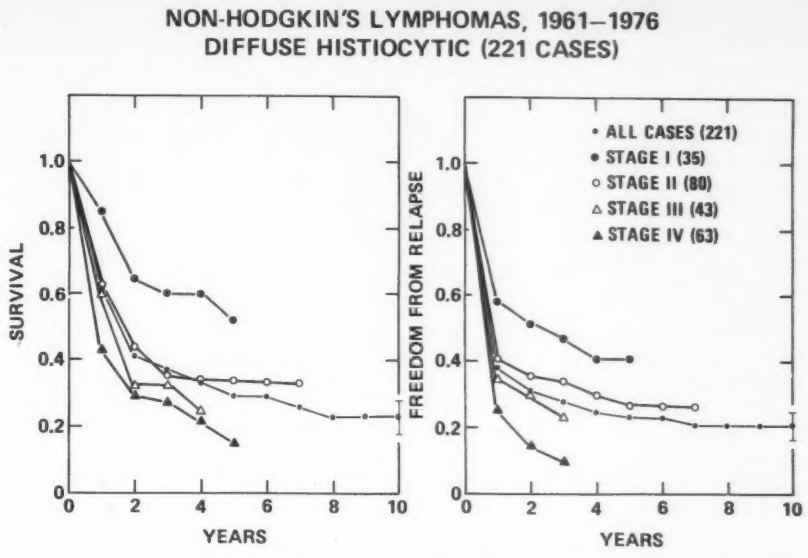

FIGURE 3.—Actuarial analysis of survival and disease-free survival of 221 previously untreated patients with diffuse histiocytic lymphoma in relation to the Ann Arbor classification.

Hodgkin's lymphomas, the validity of the E concept, the relative importance of systemic symptoms (ie, the A or B subgroups), or the distribution of the various stages for the different histologic subgroups. It is therefore not surprising that the Ann Arbor classification has only limited value for the non-Hodgkin's lymphomas and will require modification if it is to achieve the full potential of a staging classification.

Histopathologic Subgroups and Classifications

The non-Hodgkin's lymphomas are a diverse group of diseases, varying from among the most aggressive and rapidly fatal human neoplasms to among the most indolent and well tolerated. All are considered to be primary neoplasms of lymphoid tissues, and none have the characteristic giant cells and tissue reaction of Hodgkin's disease. Only in recent years has a relatively useful and acceptable histopathologic classification become available for these diseases, the Rappaport classification (7), but several new proposals (8) have made it evident that this classification has deficiencies and will undergo modification. It cannot be expected that a single system will be equally satisfactory for all the purposes of a staging classification for Hodgkin's disease and the ten or more subgroups of the non-Hodgkin's lymphomas, including some which have yet to be completely defined.

Diagnostic Procedures

The problem is further complicated by the rapidly changing and evolving methods which are used to determine the extent of disease in the lymphomas. Data from most of the reports in the literature before 1970 were not based on diagnostic laparotomy and splenectomy or even adequate bone-marrow biopsy to determine the sites and extent of disease. Even bipedal lymphography had not been used routinely in many series, and these defects make previous staging designations meaningless by current standards.

The variable natural histories of these neoplasms and their response to therapy further complicate their evaluation and classification. The aggressive behavior of some of the histologic subgroups blurs potential prognostic differences because current therapy is so inadequate for almost all the sites and extent of disease as separated by the Ann Arbor system. At the other extreme all the Ann Arbor subgroups for most of the nodular histologic types show a relatively good natural history and survival.

Figures 3 and 4 illustrate these points for diffuse histiocytic lymphomas and nodular poorly differentiated lymphocytic lymphomas respectively.

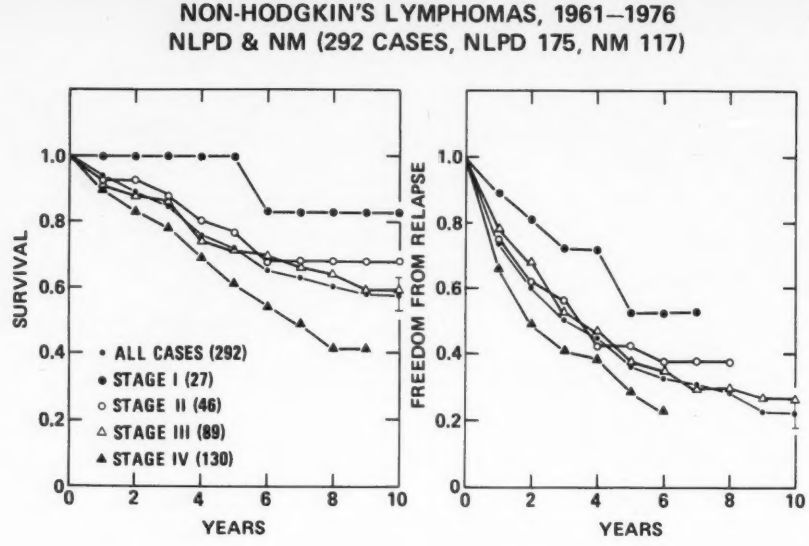

FIGURE 4.—Actuarial analysis of survival and disease-free survival of 292 previously untreated patients with nodular lymphomas in relation to the Ann Arbor classification.

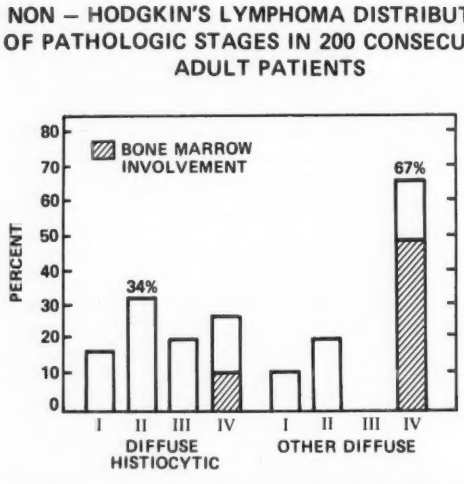

FIGURE 5.—Distribution of patients with diffuse lymphomas according to the Ann Arbor pathologic stage.

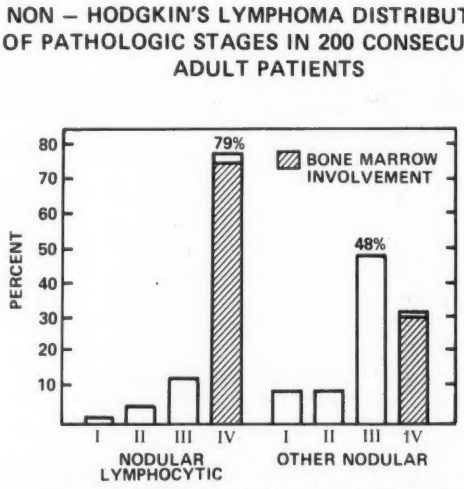

FIGURE 6.—Distribution of patients with nodular lymphomas according to the Ann Arbor pathologic stage.

Distribution of Ann Arbor Stages Among the Rappaport Subgroups

The Ann Arbor classification separates four stages of Hodgkin's disease presentation into subgroups, each of which is of relatively significant proportions. Series of patients staged with laparotomy and splenectomy contain approximately 15% stage I, 35% stage II, 35% stage III, and 15% stage IV. Almost half of the patients have systemic symptoms at presentation, and these correlate well with the extent of disease, ie, the greater the extent of disease the greater the proportion with systemic symptoms.

The variable results obtained when the Ann Arbor classification is applied to the Rappaport subgroups of the non-Hodgkin's lymphomas can be illustrated in two subgroups, those with diffuse lymphomas (fig 5) and those with nodular lymphomas (fig 6). In the nodular lymphocytic subgroup, 79% of the patients have stage IV disease and only 7% have stages I and II disease combined.

In the lymphocytic cytologic subgroups, whether nodular or diffuse, a great majority of patients will have widespread disease, ie, Ann Arbor stage IV. This is also true, by definition, for patients with chronic lymphocytic leukemia. Yet, patients with chronic lymphocytic leukemia have widely different prognoses depending on involvement of the liver and spleen or presentation with bone-marrow failure. Rai et al (6), in their data and proposals, have suggested that five prognostic subgroups can be recognized, all of which would fall within the Ann Arbor stage IV designation. This type of analysis will have to be carried out in some of the non-Hodgkin's subgroups in which the great majority of patients present with stage IV disease, and new proposals for classification will have to be tested.

Bone-Marrow Involvement

The Ann Arbor classification and recommendations for Hodgkin's disease include bone-marrow biopsy as an additional surgical procedure to determine the pathologic stage of disease (2). The procedure had not been used routinely in staging patients with Hodgkin's disease, and the yield of positive bone marrows was low, about 10%, in untreated patients.

The great value and importance of adequate bone-marrow biopsy in the non-Hodgkin's lymphomas has become appreciated since 1970, especially for the lymphocytic non-Hodgkin's lymphomas (9). This procedure should be a routine examination, equivalent to other clinical tests. It is an office procedure and should be done in virtually every patient newly diagnosed as having a non-Hodgkin's lymphoma. As such, it should not be included with laparotomy and splenectomy as a pathologic staging procedure.

Conclusions

It is premature to make recommendations concerning modifications of the Ann Arbor staging system for the non-Hodgkin's lymphomas. Agreement will first be required on modifications of the Rappaport histopathologic classification, especially for the diffuse lymphomas of large cell types and for the tumors seen in childhood. A study recently funded by the National Cancer Institute, which is working to correlate new histopathologic classifications and proposals with clinical data, should produce agreement concerning necessary modifications. When this study is completed, an international committee should be formed to review pertinent data and recommend improved staging classifications for the non-Hodgkin's lymphomas.

Until that time, however, the Ann Arbor system should be used because it serves two of the four major purposes of a staging classification. It provides a standardized system for comparative purposes and it permits uniform description in scientific communications. However, for many of the pathologic subgroups, the Ann Arbor system is seriously deficient in identifying prognostic factors and in selecting therapy.

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DISCUSSION I[1,*]

Dr. Ultmann: What conclusions can we draw from the large amount of information given to us at this session? First, we can agree that non-Hodgkin's lymphoma is *not* Hodgkin's disease. But we must also recognize that Hodgkin's lymphoma is probably not a single disease; it is probably a group of diseases or group of manifestations of a single cause. Secondly, whereas most patients with Hodgkin's disease can undergo clinical and surgical staging, many of those with non-Hodgkin's lymphoma are elderly and have medical conditions that prevent surgical staging; the staging techniques are therefore not as applicable to them. A third important point that has been reported at this symposium, and summarized in many publications, is that patients with non-Hodgkin's lymphoma present in stage IV disease more often than patients with Hodgkin's disease. Over 50% of patients can be demonstrated to have widespread disease usually due to involvement of skin, bone marrow, liver, bone, pleura, and other extralymphatic sites.

In Hodgkin's disease both positive and negative lymphangiograms (LAG) have been accepted as accurate. In non-Hodgkin's lymphoma patients, positive LAGs accurately predict that 90% of cases will have some abdominal involvement; from that it can be deduced that the spleen and the liver will be positive as well. A positive LAG also predicts a positive bone marrow. On the other hand, and this is very important in thinking about non-Hodgkin's lymphoma, when the LAG is negative, it is not as accurate in predicting absence of disease as it is in Hodgkin's disease. With a negative LAG, one must remember that this technique can not detect abnormalities of the mesenteric nodes; these may be involved in $> 50\%$ of patients with non-Hodgkin's lymphoma.

Two other techniques should be mentioned. We perform inferior vena cavagrams (IVC) during the staging workup. The IVC shown in figure 1 clearly indicates enlarged paravertebral nodes; more often oblique or lateral views are required to detect an abnormality (fig 2). Our group has shown that when positive the IVC is as accurate as the LAG. The IVC is especially useful in the upper parts of the abdomen where the LAG is not as effective. However, it must be remembered that this technique examines only the right side. In patients who might not be able to tolerate an LAG or other staging procedures, the IVC is a valuable technique (table 1).

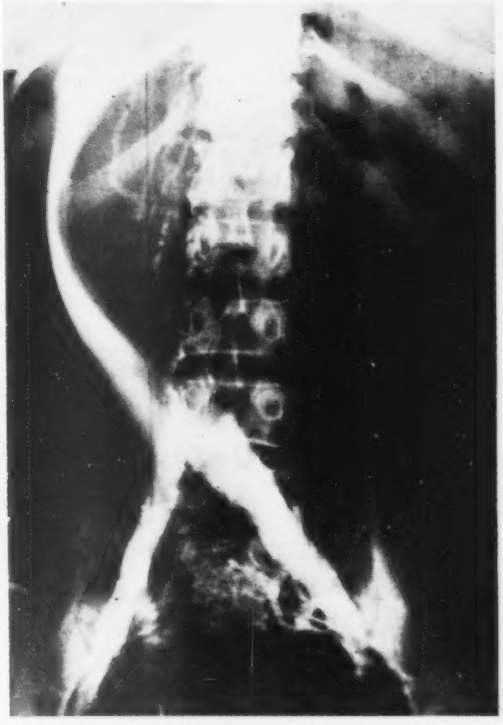

FIGURE 1.—Large, lobulated retroperitoneal mass can be seen on the IVC displacing the inferior vena cava toward the right and indenting its outline (supine view).

[1]The following investigators participated in this discussion: *S. A. Rosenberg* (chairman), *E. Glatstein*, *R. Castellino*, and *D. R. Goffinet* (Stanford University School of Medicine, Calif); *J. E. Ultmann* (University of Chicago, Ill); *Dr. Colineas* (The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston); *V. T. DeVita* and *B. A. Chabner* (National Cancer Institute, Bethesda, Md); *Dr. Arrell* (Toledo, Ohio); *Dr. Antinez* (Cleveland Clinic, Ohio); *C. D. Bloomfield* (University of Minnesota, Minneapolis); *S. E. Jones* (University of Arizona College of Medicine, Tucson); *M. Coleman* (New York Hospital, Cornell Medical Center, NY); *Dr. Crawford* (Fort Wayne, Ind); *N. Jaffe* (Sidney Farber Cancer Institute, Harvard Medical School, Boston, Mass); and *Dr. Hedsall* (Springfield, Mass).

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FIGURE 2.—Large, lobulated retroperitoneal mass is found on the IVC elevating and narrowing the lumen of the inferior vena cava (lateral view).

TABLE 1.—IVC results in 46 patients*

	Histology		Accuracy of IVC (%)
	Positive	Negative	
IVC abnormal†	13	1	93
IVC normal	17	15	47
Sensitivity of IVC (%)	43	94	

**From* Moran EM, et al. Staging laparotomy in non-Hodgkin's lymphoma. Br J Cancer 31 (suppl II):228–236, 1975. Reproduced with permission.

†Criteria for abnormal IVC are displacement or extrinsic compression.

TABLE 2.—Gallium 67 scan (30 patients, 240 sites* evaluated)†

	Histology		Accuracy of scan (%)
	Positive	Negative	
Scan positive	36	8	82
Scan negative	81	115	59
Sensitivity of scan (%)	31	93	

*Sites evaluated: cervical-supraclavicular, mediastinal, right and left axillary, right and left iliac-inguinal, para-aortic-celiac-mesenteric, splenic.

† *From* Moran EM, et al. Staging laparotomy in non-Hodgkin's lymphoma. Br J Cancer 31(suppl II):228–236, 1975. Reproduced with permission.

The gallium 67 scan has shortcomings but on occasion can be helpful. In a patient shown in figure 3, this test demonstrated a large mass between the liver and the spleen, which subsequently was proved to be a lymphoma; in this patient the LAG and IVC were negative. The accuracy of gallium 67 scanning is 82% if the scanning is positive (table 2).

The data presented at this conference and those available in the Proceedings of the London Conference (Br J Cancer 31(suppl II):228–236, 1975) summarize the clinical status and response to therapy of 1200 patients with non-Hodgkin's lymphomas. It is clear from these reports that the Rappaport classification predicts differences in clinical presentations between the nodular and the diffuse patterns as well as between the various cytologic types. In light of these real predictive advantages, I urge clinicians to continue to impress on their pathologists that if they change the pathologic classification they must come up with something at least as reproducible as the Rappaport scheme.

At this conference, Dr. Goffinet has presented results according to nodular and diffuse material, and in presenting the National Cancer Institute data, Dr. Chabner has shown the clinical outcome according to subtypes: poorly differentiated lymphocytic (PDL), mixed cell, and histiocytic lymphoma. In examining the reports from this meeting it is important to analyze the results presented by various investigators according to both histologic and cytologic classification.

If we know that cytology is PDL, mixed cell, or histiocytic, we can predict that most histiocytic lymphomas are diffuse and most PDLs are nodular (table 3). Thus, when the clinicians present data regarding nodular lymphoma, they are *not* describing histiocytic lesions. On the other hand, when they discuss diffuse lymphomas, the data will include about 20% of the PDLs and 20% of the mixed cell lymphomas, but about 90% of the histiocytic lesions.

The cytologic characteristics tend to predict the clinical or pathologic stage (table 4); for instance, if a lymph node biopsy shows histiocytic lymphoma, there is a two to three times greater chance of finding local disease than if the biopsy shows PDL

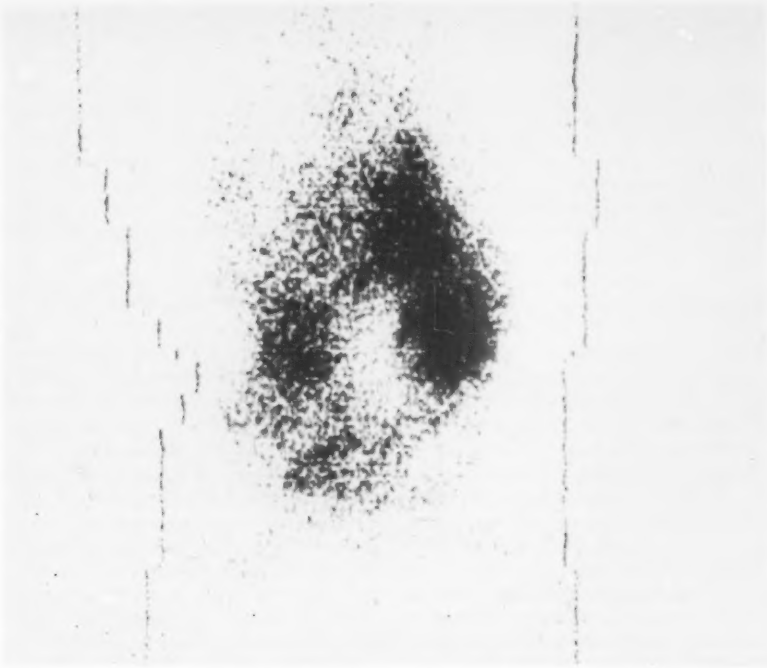

FIGURE 3.—Gallium 67 scan performed 72 hrs after the iv administration of 5 millicuries. This case demonstrates abnormal uptake in an enlarged spleen and inhomogeneous uptake over the liver; there is a large retroperitoneal mass lying between the liver and the spleen.

TABLE 3.—Distribution of nodular pattern in various non-Hodgkin's lymphomas

	% nodular
PDL	81
Mixed cell	78
Histiocytic	10

TABLE 4.—Distribution of stage in various non-Hodgkin's lymphomas

	%	
Stage	PDL/mixed cell	Histiocytic
I and I_E	4	16
	12	37
II and II_E	8	21
III	20	20
	88	63
IV	68	43

or mixed cell lymphoma. In the former situation the clinician will attempt to prove local disease; hence he will perform a laparotomy more often in patients with histiocytic lymphoma.

In contrast, if it is known that the cytology is PDL or mixed cell, a thorough search should be made for bone marrow involvement because, regardless of apparent clinical stage, the bone marrow will be involved in a significant number of patients (table 5). Furthermore, if the patient already is in stage III as determined by other clinical criteria, the incidence of bone marrow involvement rises to 80% for PDL. Similar reasoning may be applied in searching for liver involvement in patients with PDL or mixed cell lymphoma.

I believe that we can now evolve guidelines for clinical staging applicable to patients with non-Hodgkin's lymphoma which take into consideration some of the factors I have alluded to, namely, age, medical status, and the frequency of stage IV disease according to the histology and cytology on the first biopsy. Knowing the distribution of disease

TABLE 5.—Distribution of bone marrow involvement in non-Hodgkin's lymphomas

	% bone marrow involvement
PDL/mixed cell	54
Histiocytic	14

helps to predict that patients with nodular disease (which most often is PDL and mixed cell) will be less likely to benefit from the information secured from laparotomy. On the other hand, in patients with disease shown on first biopsy to be diffuse, and especially if it is of histiocytic type, laparotomy is more likely to give important information.

In addition, treatment strategy will determine whether the patient will receive laparotomy. For example, in children who will definitely receive chemotherapy, staging is done only to identify and remove bulky disease. The stage of the disease, whether I, II, III, or IV, is not going to make any difference in management decisions.

Lastly, I would like to stress the importance of restaging to verify complete response (CR). This will be particularly important if it is shown that a CR as demonstrated by accurate restaging is predictive of long-term disease-free survival, whereas clinically determined CR is not.

Dr. Colineas: Dr. Tubiana said that bulkiness or tumor size does not make any difference in prognosis. As you pointed out, this is limited to patients whose disease presents in the digestive tract or respiratory tract and who are stage I and II, and I assume they are treated with radiation. At the Toronto meetings, I described our study of the effect of 13 prognostic factors in a series of stage III and IV non-Hodgkin's lymphomas treated with different regimens. Of these, tumor size or bulkiness was the single most important factor in predicting response to chemotherapy and survival. Thus, tumor bulk has to be considered, especially since staging either as stage III or IV didn't affect response or survival.

Dr. Rosenberg: Those are important data. The rather narrow study I presented was confined to stage I or II disease of the upper respiratory and digestive tracts. There was wide variation in the tumor size, and in that special setting, bulk made absolutely no difference. However, in different stages of disease, or even different histologies and sites, mass may be a significant factor.

Dr. DeVita: May I ask Dr. Ultmann and perhaps you, Dr. Rosenberg, where you think we are going with staging laparotomy in diffuse histiocytic lymphoma that appears to be localized? You indicated that we are accumulating important data. Much of the data that I saw suggested that in spite of the fact that no disease is found at laparotomy in stages I and II, the disease recurs, so we conclude that "localized" diffuse histiocytic lymphoma is not truly localized. It appears we need some form of systemic treatment to go with radiation therapy. If that is the case, should we not go in that direction rather than continue with routine staging laparotomy?

Dr. Rosenberg: A staging laparotomy in our series showed that about 30% of those with diffuse histiocytic disease change their stage. About half are down-staged into stage I or II and the other half advance into stage III or IV. There is still a reasonable salvage rate in patients with stage I or II disease treated with radiotherapy alone, although results are better in stage I than in stage II. In diffuse histiocytic lymphoma that is surgically staged we can achieve prolonged disease-free survival in the range of 50%–80%, depending on the stage. However, that may not be good enough because chemotherapy may be able to improve even these results. I believe that the more localized the diffuse histiocytic lymphoma seems to be, the more important it is to prove that this disease is truly localized and to treat the patient with radiation. In about 30% of patients with diffuse histiocytic lymphoma, laparotomy will help in making that decision.

Dr. DeVita: That may be true of stage I, but for stage II the disease-free survival is about 25%. If a patient has stage II disease, and if you know that in surgery you are unlikely to find additional disease outside the initial nodal fields, that patient should be treated with something else. Perhaps you can still make a case for stage I, but once two lymph node areas are involved, the prognosis is so poor that it really doesn't require a laparotomy. I would not want to see everybody moving in the direction of more laparotomies in that group of patients; perhaps we should plan to do fewer.

One further point. In staging, Dr. Jaffe mentioned the use of lumbar puncture in staging children with lymphoma. I think it's a good idea. In our patients with bone marrow involvement we have noted a high incidence of central nervous system (CNS) lymphoma, particularly in the diffuse histiocytic group. We now include a lumbar puncture in all the routine staging procedures and, in fact, we recommend CNS prophylaxis when a child with the disease has bone marrow involvement.

Dr. Ultmann: Dr. DeVita probably is correct that the volume of lymphoma determines in part the outcome of the disease. In 20 patients with diffuse histiocytic lymphoma in whom accurate staging had delineated stage I and II disease and who had

received curative radiotherapy, we found that 17 were in CR with a remission duration estimated to approximate 4 years; the three who were not in remission had stage II disease with more than three lymph node sites involved at presentation. All stage I patients are controlled.

With regard to Dr. DeVita's second point, we have now treated 30 patients with histiocytic lymphoma (20 in a prospective protocol and ten off protocol) with cyclophosphamide, vincristine, methotrexate, leucovorin, and cytosine arabinoside (COMLA), and none of these patients has had CNS complications from his lymphoma. It appears that the type of chemotherapy used may in part determine which patient gets the CNS complications. For example, in the C-MOPP[2] program used by Dr. DeVita et al for the histiocytic lymphomas, they saw more CNS disease than we see with COMLA. This, I think, is a very important issue, focusing in part on the effectiveness of various agents in general and in part upon the penetration of the blood-brain barrier by specific agents.

Dr. Arrell: Will computerized axial tomography (CAT) take the place of LAGs, IVCs, or any of the other staging studies?

Panel: CAT scanning holds promise in certain areas, particularly high in the abdomen where the LAG frequently doesn't fill the nodes. In our hands, however, low in the abdomen between the aortic bifurcation and the inguinal ring, the CAT scan has not been as accurate as we would like, perhaps because we haven't had enough experience.

Dr. Glatstein: We radiate the whole abdomen with a technique that involves treating anteroposteriorly initially and then using lateral portals to treat the periaortic nodes yet spare the kidneys. Usually we have to inject IVP dye and take a lateral film to see where the kidneys are in relation to the periaortic nodes so we can miss them. Here the CAT scans would be a big help because they would help place the kidneys in relation to the periaortic nodes.

Dr. Castellino: Dr. Arrell's question is a good one. The era of CAT scanning is upon us. This technique has raised a lot of false optimism. We have to remember that detection of disease with the CAT scan and ultrasound depends upon bulk, so these are quite useful when dealing with bulky disease. The LAG can detect tumors in normal-sized lymph nodes and potentially is much more sensitive. Furthermore, with the LAG, the lymph nodes remain opacified for many months and it's much easier to follow-up a patient with a KUB than to do serial slices with these two other techniques. As noted earlier, the region between the diaphragm and the renal pedicle is a blind area to lymphography, and this is the one area where the CAT scan may have a role. I would like to emphasize that ultrasound is a good technique in this area. It is non-invasive, it is much cheaper to perform, and it delivers no radiation to the patient. Finally, you can perform these studies very quickly and with ultrasound you can actually see what you're doing. Definitive studies have yet to be done, but I do not think CAT scanning will make a major breakthrough in the detection of occult disease.

Dr. Antinez: At the Cleveland Clinic we find CAT scanning extremely useful. In the future it may play a role in the staging of Hodgkin's and non-Hodgkin's lymphoma, mainly as a guide to liver biopsy. We are able to detect very small areas of different density within the liver, and under the screen you can direct the tip of the biopsy needle exactly to the suspicious area. With its assistance, the yield of positive biopsies is very high.

Dr. Bloomfield: Dr. Jones, you did splenectomies in three patients with diffuse disease, two of whom were involved at the time of restaging. Did you do the restaging because they still had enlarged spleens?

Dr. Jones: Actually, those patients had suspicious abnormalities on liver-spleen scan.

Audience: I may have missed the point, but during staging how many sites should be routinely sampled during bone marrow biopsy?

Dr. Rosenberg: The data from the National Cancer Institute and other studies show that two sites are better than one. One might ask also whether three sites are better than two. In our series at Stanford, if we have one good biopsy we do not get a great deal more information with a second even large surgical core. Therefore your decision depends somewhat upon the quality of the first biopsy. You saw earlier in the National Cancer Institute data that only one of the two bone marrow sites was involved in about 25% of their patients. The additional yield in our study, with a second large biopsy, was 11 of 100 operated patients. There was a discordance, however, because in half of the instances the positive biopsy would have been the first biopsy. Perhaps Dr. Bloomfield would like to comment.

Dr. Bloomfield: We now do four marrow sites at diagnosis and we even pick up a few additional patients where we are getting one out of four.

Dr. Goffinet: I can give you some numbers on the Stanford series comparing open and needle biopsies. One hundred and sixty-one patients had adequate but benign needle biopsies and the open iliac crest marrow was positive in 18 of these. Thus, the rate

[2]C-MOPP = cyclophosphamide, vincristine, prednisone, and procarbazine.

of false negatives with a single bone marrow needle biopsy is around 10% or perhaps a little more.

Dr. Ultmann: Our data indicate that it is useful to sample more than one bone marrow site. Of 93 patients, 53 had one biopsy and 26 of these were positive; all were PDL and mixed cell lymphomas. The remaining 40 patients had two or more bone marrow specimens examined and 26 were positive. Since this is a relatively simple procedure and the implications for therapeutic strategy of finding marrow involvement are great, we biopsy at two sites but in two directions each, obtaining four specimens.

Dr. Coleman: Let us say we have a patient whom we stage clinically as stage II and on whom we don't do a laparotomy. He turns out to be a stage IV patient. Have we lost anything by not treating this patient early? If we gave regional radiotherapy and let him go home and relapse, do we benefit him by getting to him earlier with chemotherapy? In other words, is there any material benefit in finding out that the patient has stage IV disease at the time of initial staging?

Dr. Ultmann: This is a question each of us faces every day. In part, the answer depends on what you are going to do with the information you have obtained up to that point. With histiocytic disease, for example, we believe that if it is proved to be of limited extent, we have a good chance to cure with radiotherapy. If your strategy dictates that you're going to give total nodal therapy to disease that appears to be limited clinically and you make a mistake in your clinical estimate, what have you lost? Most series indicate that it is very difficult to administer aggressive chemotherapy for diffuse lymphomas, either histiocytic, PDL, or mixed cell, after total nodal radiotherapy. Therefore, determining the correct stage is an important decision which you should make at the beginning.

Dr. Coleman: Most people appear to accept stage III disease as being fairly diffuse and proceed with chemotherapy. As a general rule, most stage III lymphomas do not get total nodal irradiation; in fact, most people are not willing to commit themselves to radiotherapy beyond extended field, if that much. Thus it seems that no one has shown that getting to these patients early with chemotherapy would benefit them. Our own experience with the morbidity in the staging laparotomy seems to indicate that it is a formidable procedure.

Dr. Rosenberg: I don't think the latter statement is true if you select your cases. In Dr. Goffinet's series the morbidity is now down to 5% and he has had no deaths in the last group of > 100 patients. I must disagree with you. If you have a responsive disease such as any of the lymphomas and have the chance to cure with chemotherapy, it seems logical, though not always proved, that you should use that therapy as early as possible when the disease is minimal and the patient is in the best possible condition. If that makes sense, as I think it does, then I see no reason for delaying treatment and waiting for progression of usually rapidly fatal disease to prove it requires chemotherapy.

Audience: I have two questions. First, what do you do with patients on whom the surgeon has done a biopsy of an abdominal mass without the proper staging procedures? Secondly, how do you resolve a questionably positive LAG at the time of restaging? By a second laparotomy?

Dr. Goffinet: We do a peritoneoscopy if the surgeon didn't do a very good laparotomy. In addition, we frequently repeat our LAGs. One of the advantages of completing a systematic staging procedure before therapy is that if you have equivocal LAGs after therapy in patients who had bone marrow or liver involvement initially, you go back and biopsy those sites again. Frequently you find residual disease in those extralymphatic sites. This indicates that the patient needs further therapy.

Dr. Rosenberg: Your question is of great practical importance. We should plead for the co-operation of surgeons in this aspect of management. Although most pathologists agree that frozen sections are unsatisfactory for final diagnosis and classification of the lymphomas, in most instances a frozen section can give a reasonable indication that the patient has a lymphoma and not an epithelial tumor.

We should try to persuade our surgical colleagues, who often have to deal with an emergency situation, that if the diagnosis of lymphoma is likely from a frozen section, he should do a reasonable staging procedure. In addition to dealing with the emergency he should, for example, perform a liver biopsy and examine the spleen. The spleen should be removed if it is grossly abnormal and the conditions permit that procedure. It would be desirable to obtain an adequate bone marrow biopsy while the patient is under anesthesia. If these measures were taken, along with a good operative description, most of the needed staging information would be available. Also, the radiotherapist would be grateful if the mass were outlined with clips, because we're often left with a vague description for patients who may have presented with intussusception or an abdominal mass.

Audience: At the M. D. Anderson Hospital the Radiology Department is aggressive and surgically oriented. The staff frequently helps us resolve questionably positive LAGs by doing a lymph node aspiration with a very long 23-gauge needle. They

send the specimens to the Cytology Department and the pathologists are frequently able to tell us whether a tumor is present or not. They won't specify the histology, but they can tell whether or not there is lymphoma in that lymph node. The aspiration is a benign procedure and we haven't had any complications from doing this kind of aspiration biopsy.

Dr. Chabner: Dr. Rosenberg, in your discussion of the problems inherent in using a staging classification, you concluded that neither classification, as currently constituted, carried an advantage in terms of prognosis and choice of therapy, particularly in making a distinction between stage III and IV disease. However, this classification has one important implication: if you really believe there is a difference between stages III and IV, it's important to establish that difference, but in the process you will end up doing a laparotomy on people who have positive LAGs and no other evidence of disease. I don't believe laparotomy in these people is justified because there is a high yield of disease outside the fields of radiation and a fairly substantial yield in the liver as well. Do you believe it is justifiable to do laparotomy on patients with stage III disease and, secondly, is it important to preserve the distinction between stage III and IV?

Dr. Rosenberg: I don't think it's absolutely established that there is no difference in prognosis between stage III and IV disease, pathologically staged and treated with chemotherapy for example, although I have a feeling that for the majority of the Rappaport subgroups there is no difference. One should not do staging laparotomies for stage III patients, at least when the LAG is grossly positive (though in some it will be equivocal). Nevertheless, there still is a need to prove the point, and perhaps Stanford will be the last institution to abandon laparotomy for stage III patients and by doing so we'll help prove the point. There may be one or two histologic subgroups that may be confined to the lymph nodes, but I would guess that these would constitute a small fraction of the cases and they will not be lymphocytic lesions.

Dr. Crawford: Dr. Jaffe, in approximately what percentage of children with non-Hodgkin's lymphoma is CNS relapse the prime cause of death? Also, what dose level did you use for prophylaxis?

Dr. Jaffe: Very few patients with non-Hodgkin's lymphoma relapse in the CNS. Unfortunately, spinal taps were not done routinely in the initial review of the 244 patients but, as I recall, approximately 20% did manifest CNS involvement in one form or another. As far as the CNS prophylaxis is concerned, we use 2400 rads of cranial irradiation plus 12 mg/m^2 of intrathecal methotrexate twice weekly for five injections during the period of cranial irradiation. The cranial irradiation was performed by our radiation therapist, Dr. Caskie.

Dr. Hedsall: As Dr. DeVita mentioned, patients with diffuse histiocytic lymphoma, who form the great majority of those with diffuse disease, eventually go on to develop disseminated disease, and those with nodular "favorable" histologies, even if they are found to have stage IV disease, go on to have a favorable outcome with single-agent chemotherapy. If this is true, should the oncologist in the community hospital submit his patients to a staging laparotomy when he might only encounter a few during the course of a year?

Dr. Ultmann: I am sympathetic with your problem. In this symposium we are trying to share with you the data we have obtained by a systematic approach in research centers. You have asked how these data are applied, for example, in your home town of Springfield, Mass. If you treat all patients who have histiocytic lymphoma with systemic chemotherapy because you do not have an experienced radiotherapist to give radiation that might achieve a cure (eg, mantle therapy or total nodal), then you don't need to stage. On the other hand, if you believe there is a role for radiotherapy in histiocytic lymphoma, and if your community has an experienced radiotherapist, you would do your patient a disservice if you undertook such therapy for histiocytic lymphoma in the neck without having proved to your own satisfaction that the patient is not one of the 14% of patients who have occult bone marrow involvement, or the 14%–20% who have liver involvement. Patients in these groups, of course, should not be treated by radiation. You are correct in saying that the data presented at this meeting suggest that in nodular lymphoma, except for experimental studies, you have little reason to stage when there is clinical evidence of stage III nodular lymphoma.

We have evidence to suggest that in both the diffuse and the nodular lymphomas the ability to achieve a clinical CR has a profound effect upon ultimate survival. There is an important difference between a patient with a nodular lymphoma who achieves a CR and one who achieves only a partial remission, and one of the advantages of staging before treatment is that you then have a better baseline against which to measure the effectiveness of your therapy.

DISCUSSION II: Roundtable Discussion of Histopathologic Classification [1,*]

Dr. Berard: Dr. Rappaport will review the current status of nomenclature, terminology, and clinicopathologic correlations of the various classifications that have been proposed for the non-Hodgkin's lymphomas.

Dr. Rappaport: Twenty years ago we became convinced that the nodular lymphomas (the so-called follicular lymphomas) or the conditions that had been called Brill-Symmers disease were not a homogeneous group (1). While all of the lesions had a nodular pattern, there were differences in the cellular composition, which were equally evident in malignant lymphomas with a diffuse pattern. Later the classification we had proposed on purely morphologic grounds (2) was taken up by our clinical colleagues because they found that it gave clinically useful correlations. However, since then it has been noted to have scientific flaws (3–5). These we acknowledge and we welcome the efforts which have been discussed during this symposium to clarify the problems we face in both classification and nomenclature. I have no new classification to propose at this time; I am here merely to ask questions, some of which I hope will prove challenging.

Two classifications have been introduced that use a functional approach: one, by Lukes and Collins (3), has already resulted in an interesting conceptual reorientation; the other, by Lennert and associates (4), is beginning to find acceptance in some European countries and is being employed in clinical studies such as the one conducted in Essen, Germany (6).

When discussing classification, one cannot ignore nomenclature because the same word may not mean the same thing to all people. Let us start with the term "non-Hodgkin's lymphoma." You will not find it in a textbook of pathology. Rosenberg has said it is an unfortunate term, but I can live with it. I believe it expresses what it means and it is probably better than "malignant lymphoma, noncleaved follicular center cell type" (3) employed for one of its subgroups. The Kiel classification (7) also uses a functional approach, as is evident from the use of the words "immunocytic" and "immunoblastic." It shares with Lukes' classification the word "center," using terms like "centrocytic," "centroblastic," and "centroblastic-centrocytic." On the surface these two classifications appear similar but, in fact, they are very far apart.

In a recent publication (4), Lennert et al have listed the relative frequency of the various types of non-Hodgkin's lymphomas (table 1), and all cases of malignant lymphoma-lymphocytic type, except for a small group of cases of "hairy cell leukemia" (0.4%) and of Sézary syndrome and mycosis fungoides (1.4%), were in fact chronic lymphocytic leukemia (20.7%). Here we have to make a decision: are we going to include chronic lymphocytic leukemia among the non-Hodgkin's lymphomas? As Dr. Rosenberg has pointed out this afternoon, we have to apply to the leukemias different staging criteria from those employed for the malignant lymphomas in order to assess the extent of the disease and to distinguish between clinically slowly progressive and clinically aggressive forms. For chronic lymphocytic leukemia for instance, anemia, severe lymphocytosis, and thrombocytopenia are important criteria for the recognition of advanced disease which is not the case for non-Hodgkin's lymphomas. Thus, including chronic lymphocytic leukemia among the non-Hodgkin's lymphomas does not seem to be clinically useful.

The main points of the Lukes-Collins classification (3) are that cellular function can be recognized morphologically and that such function should constitute the main criterion for classification and nomenclature. Further, Lukes affirms that "convoluted lymphocytic lymphoma" is a distinct clinicopathologic entity, that nodular lymphomas and their diffuse counterparts originate in follicular centers, and that the pattern, nodular versus diffuse, has no prognostic significance. Finally, he believes that, with rare exceptions, the "histiocytic" lymphomas present the features of transformed lymphocytes and that the majority of such tumors are composed of cells identifiable as large, noncleaved, follicular center cells.

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[1]The following investigators participated in this discussion: *C. W. Berard* (chairman) and *E. Jaffe* (National Cancer Institute [NCI], Bethesda, Md); *H. Rappaport* (University of Chicago School of Medicine, Ill); *R. Lukes* (University of Southern California School of Medicine, Los Angeles); *M. Seligmann* (Hôpital Saint-Louis, Paris); *C. Bloomfield* (University of Minnesota School of Medicine, Minneapolis); *R. Dorfman* (Stanford University School of Medicine, Calif); *G. Byrne* (University of Miami School of Medicine, Fla); and *M. Shaw* (University of New Mexico, Albuquerque).

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TABLE 1.—Frequency of malignant lymphomas in routine material of the Lymph Node Registry, Kiel, 1966–73*

Diagnosis	No. of cases	Lymphomas (%)	Non-Hodgkin's lymphomas (%)
Hodgkin's disease	641	43.0	—
Malignant lymphoma-lymphocytic	184	12.3	21.6
Chronic lymphocytic leukemia	176	11.8	20.7
"Hairy cell leukemia"	3	0.2	0.4
Sézary syndrome and mycosis fungoides	12	0.8	1.4
Malignant lymphoma-lymphoplasmacytoid (immunocytic)	129	8.6	15.2
Malignant lymphoma-centrocytic	72	4.8	8.5
Malignant lymphoma-centroblastic/centrocytic	184	12.3	21.6
Malignant lymphoma-centroblastic	3	0.2	0.4
Malignant lymphoma-lymphoblastic	114	7.6	13.4
Burkitt type	6	0.4	0.9
Convoluted type	7	0.5	0.8
Others	101	6.3	11.1
Malignant lymphoma-immunoblastic	134	9.0	15.8
Plasmacytoma (extramedullary)	7	0.5	0.8
Epithelioid cellular lymphogranulomatosis (lympho-epithelioid cellular lymphoma)	23	1.5	2.7
Unclassifiable	120	—	—
Total	1618	—	—

*From Lennert et al (4).

We take no exception to the contention that the large-cell nodular lymphomas and their diffuse counterparts originate from follicular center cells and that most of the so-called histiocytic lymphomas are of lymphoid origin (8). However, there are certain aspects of the two new classifications which I would like to discuss.

With respect to the Lukes-Collins classification, it should be noted that information published to date has not included the numerical distribution of their subdivisions of non-Hodgkin's lymphomas. During this symposium Lukes gave a numerical distribution; he told me later, however, that this does not represent the true distribution but is only the distribution of the cases he had an opportunity to study. Moreover, we do not have actuarial survival data that would give us some indication as to the clinical significance of the Lukes-Collins classification.

Now let us look at the classification in detail. Barcos and Lukes (9) made an important contribution when they called attention to the existence of a peculiar convoluted lymphocyte that so frequently is associated with a malignant lymphoma with a characteristic clinical, pathologic, and hematologic picture. Often, but not always, this lymphoma is of mediastinal origin, has a distinctive sex distribution, has a tendency to early diffuse marrow infiltration, and is associated with the presence of tumor cells in the blood. Some of the cells in this tumor have convoluted nuclei, but they have another feature which deserves equal emphasis, namely, in tissue sections the cells exhibit marked immaturity and considerable mitotic activity. These cells are, in our experience, indistinguishable from the lymphoblasts of acute lymphoblastic leukemia. In our material, Nathwani et al (10) found that in 14 of 30 cases, the tumor cells did not contain convoluted nuclei but showed an equally prominent mitotic activity and cellular immaturity. These tumors composed of immature lymphoid cells with non-convoluted nuclei also had the same tendency to progress rapidly. The absence of nuclear convolution could be confirmed by an electron microscope. There appear to be no clinical differences between the convoluted and the non-convoluted forms of lymphoblastic lymphoma. We became aware that in the past we had erroneously included these "lymphoblastic" tumors either among the poorly differentiated lymphocytic lymphomas or the undifferentiated lymphomas or both. We recognize now that they do deserve a separate position in the scheme of malignant lymphomas. However, this raises an important question: is the lymphoblastic lymphoma always a T-cell lymphoma, and if so, is nuclear convolution a distinctive morphologic marker for T-cells? These lymphoblastic lymphomas have been shown to possess an interesting histochemical marker, namely, an acid-phosphatase-positive paranuclear clump near the Golgi zone (4), but we do not as yet know whether this is a consistent feature for T-cell lymphomas.

Cells with convoluted nuclei can be recognized both in this entity and in cases of acute lymphoblastic leukemia which do not have the clinical manifestations of a lymphoblastic lymphoma such as the bulky masses.[2] Undoubtedly, lymphoblastic lymphomas have been included in series of acute lympho-

[2] Pangalis GA, Nathwani BN, and Rappaport H. The significance of nuclear convolution in acute lymphoblastic leukemia. In preparation.

blastic leukemia if they presented first with abnormal blood findings; however, malignant lymphomas of the lymphoblastic type differ from acute lymphoblastic leukemia in several respects. For example, in 29 of our 30 cases, the total platelet count was initially $> 150{,}000/mm^3$ (10), while in acute lymphoblastic leukemia, according to Wintrobe et al, 93% of all patients had pronounced thrombocytopenia at the time of admission (11). Thus there is a difference although it is not necessarily morphologic or microscopic. We believe that malignant lymphoma-lymphoblastic type deserves a special place in the classification of malignant lymphoma irrespective of whether the cells have convoluted nuclei, whether it occurs in children and young adolescents or in adults, whether it has a predominantly male sex distribution, and whether it has a mediastinal presentation (10).

In this respect, our concept and that of Lennert et al seem to be in accord except that I do not know how they obtained such a large number of lymphoblastic lymphomas in their series, namely 114 out of 977, or 13.4% of all their non-Hodgkin's lymphomas (4). We found that in our series (10) only 3% belonged to this category. Of Lennert's 114 lymphoblastic lymphomas, six were of the Burkitt's type and seven were of the convoluted type. The rest, 101 cases, are listed under "others" (4). Perhaps Dr. Lukes can tell us to what group in his classification those that Dr. Lennert lists as "others" belong.

Among the T-cell malignant lymphomas, Lukes has included mycosis fungoides and Sézary syndrome. There is no argument about this; it is an established fact that mycosis fungoides and Sézary syndrome are histologically and cytologically distinctive disorders. On the other hand, Lukes has alluded to the fact that his group is learning how to recognize not only the convoluted lymphocytic lymphoma as a morphologically distinctive disorder of the T-cell type, but also immunoblastic sarcoma of T-cell type. From his publications and lectures we have not been able to learn how to identify immunoblastic sarcoma of the T-cell type and would be anxious to learn it.

One question, however, has bothered me. Are mycosis fungoides, including Sézary syndrome, convoluted lymphocytic lymphoma, and T immunoblastic lymphoma the only three existing T-cell tumors? We recently observed a T-cell lymphoma composed of large and small lymphoid cells which would probably have been called "mixed cell" type according to the classification of Rappaport, in which the great majority of both large and small lymphoid cells were T-cells (8). Are there perhaps other T-cell lymphomas which do not fulfill the morphologic criteria of the three categories listed in the Lukes and Collins classification under T-cell type? Is it prognostically meaningful to recognize a lymphoma as T-cell type rather than as the disease entity which it represents, such as mycosis fungoides, Sézary syndrome, or lymphoblastic lymphoma (3)? Where do we place cases interpreted morphologically as T-cell or B-cell lymphomas in which surface marker studies reveal that the tumor cells are, in fact, null cells? Brouet and associates for instance have shown that malignant lymphomas composed of large cells called malignant lymphoma-histiocytic type according to the Rappaport classification may either show B-cell markers, T-cell markers, or no markers (5). Are these morphologically distinguishable? If not, are we required to do surface marker studies on all of them? How can we practically distinguish B immunoblastic from T immunoblastic lymphomas? And, even if we could, is any clinical significance of such a distinction presently known?

Now we shall turn to the small lymphocytes and the neoplasias composed of them. In the Lukes-Collins classification these tumors carry the term "small lymphocyte (chronic lymphocytic leukemia)" and Lukes has indicated that the small lymphocytic, B-cell type lymphoma is the tissue expression of chronic lymphocytic leukemia. This goes well with Lennert's assertion that well-differentiated lymphocytic lymphoma is always chronic lymphocytic leukemia (4). Dr. Lukes tells me privately that he no longer thinks so, and when I look at his classification presented at this symposium I see already a considerable improvement. The small lymphocyte now appears under both T-cell and B-cell categories. Everybody erred several years ago when it was not recognized that small lymphocytes may also give rise to a T-cell neoplasm. Chronic lymphocytic leukemia of T-cell type now seems to have a characteristic appearance in the peripheral blood. The lymphocytes are often particularly rich in azurophilic granules and, in all 11 cases reported by Brouet and associates (12), the cells had a consistently high content of β-glucuronidase and acid phosphatase. Other distinctive features were massive splenomegaly (five patients), cutaneous lesions (four patients), and severe neutropenia (four patients).

Now the question may be raised: is well-differentiated lymphocytic lymphoma always a manifestation of chronic lymphocytic leukemia? An imprint would indicate to the hematologist that the cells are identical with the mature-appearing lymphoid cells of chronic lymphocytic leukemia. Pangalis et al analyzed 108 such cases, all of whom first had a lymph node biopsy (13). (In other words, when the lymph node biopsy was done, either there were no evident abnormalities in the peripheral blood or

their significance was not recognized.) Among these 108 cases there were 41 who had neither a monoclonal gammopathy nor an absolute lymphocytosis (> 4000 cells/mm^3). Twenty others had a monoclonal gammopathy but no absolute lymphocytosis was present in 18 of the 20. The remaining 47 had absolute lymphocytosis and no monoclonal gammopathy and were classified as chronic lymphocytic leukemia. Analyzing the 41 patients without monoclonal gammopathy and without absolute lymphocytosis (well-differentiated lymphocytic lymphoma group), we found that in 11 the bone marrow was negative, in 24 it was positive, and in six it was not available. Of the 11 in whom it was negative, only one subsequently developed lymphocytosis; this happened 80 months later and the total cell count was 54,100/mm^3. Of the 24 who had bone marrow involvement at the time of lymph node biopsy, only four developed lymphocytosis, two of them to only a moderate degree. In all four, lymphocytosis developed within the first 2 years. Thus, we have no evidence that a malignant lymphoma of the well-differentiated lymphocytic type is necessarily a manifestation of chronic lymphocytic leukemia. When a patient with well-differentiated lymphocytic lymphoma develops bone marrow involvement, it is just that—bone marrow involvement by well-differentiated lymphocytic lymphoma and not necessarily chronic lymphocytic leukemia.

The median survival of the patients with well-differentiated lymphocytic lymphoma was 124 months compared to 58 months for those with monoclonal gammopathies and 78 months for those with chronic lymphocytic leukemia. The only difference between the well-differentiated lymphocytic lymphoma group and the chronic lymphocytic leukemia group was that in our series, the patients with chronic lymphocytic leukemia, as is well known, often had hypogammaglobulinemia, which made them perhaps more susceptible to infection, while patients with well-differentiated lymphocytic lymphoma without absolute lymphocytosis rarely had hypogammaglobulinemia. We consider these three groups (well-differentiated lymphocytic lymphoma, chronic lymphocytic leukemia, and well-differentiated lymphoproliferative disease with monoclonal gammopathy) to be manifestations of a spectrum of closely related B-cell lymphocytic proliferation (13,14), excluding of course, the rare T-cell chronic lymphocytic leukemia.

Lukes and Lennert both believe that the type of B-cell lymphoma characterized by a plasmacytoid lymphocyte should be placed in a separate category. Lukes called it "plasmacytoid lymphocyte lymphoma" and Lennert has recently called it "immunocytoma." In these patients the small lymphocytes usually secrete immunoglobulin into the serum in demonstrable amounts, while in chronic lymphocytic leukemia and well-differentiated lymphocytic lymphoma, the monoclonal immunoglobulins are detected as a rule on the cell surface only. In the case of so-called immunocytomas, the immunoglobulin, IgM or rarely IgA, is demonstrable in the cytoplasm (and sometimes in the nucleus) as PAS-positive material. When you look carefully you see that the majority of the lymphoid cells are small lymphocytes and variable numbers of them are plasmacytoid and pyroninophilic. I would like to ask Dr. Jaffe why, when we look at cases of Waldenstrom's macroglobulinemia and other monoclonal gammopathies, we see all the transitions between the small lymphocytes on the one hand and the plasmacytoid lymphocyte and plasma cell on the other, but no immunoblasts. We suggested that these lymphocytes deserve the term "well-differentiated," because in pathology we apply this term to tumor cells which closely resemble their non-neoplastic counterparts morphologically and functionally, as for instance the cells of a well-differentiated adenocarcinoma. In their publication (4), Lennert et al placed great emphasis on the absence of plasmacytoid features and of PAS-positive material in any lymphocytic lymphomas other than an immunocytoma. We have found plasma cells and/or plasmacytoid lymphocytes in both chronic lymphocytic leukemia and well-differentiated lymphocytic lymphoma, without any evidence of monoclonal gammopathy (13). In monoclonal gammopathy we found intracellular PAS-positive material in only 65% of the cases. However, PAS-positivity was also found in 27% of the cases of well-differentiated lymphocytic lymphoma and 23% of those with chronic lymphocytic leukemia, and in neither was there monoclonal gammopathy. Thus, there is a considerable overlap between (*a*) the well-differentiated lymphocytic lymphoma, (*b*) the predominantly lymphocytic monoclonal gammopathies, and (*c*) chronic lymphocytic leukemia.

We come now to Lukes' small cleaved follicular center cell tumor or the centrocytic lymphoma of Lennert. In 1956, we described these cells as angulated and indented (1). I did not use the term "cleaved," which is more daring though apparently grammatically incorrect, as had been pointed out recently (15).

Lukes recognized nuclear indentation as an indication of follicular center origin, whereas I did not (1). In his classification Lukes refers to follicular center cell types of lymphoma and divides them into follicular, diffuse, follicular and diffuse, and sclerotic (3). Lennert and associates in the Kiel classification (7) divided them into follicular, follicu-

lar and diffuse, and diffuse, but in their more recent publication (4) they no longer use this subdivision. All cases of malignant lymphoma of the centrocytic type, which is considered by Lennert to be synonymous with the small cleaved follicular center cell tumor of Lukes, are diffuse, while the malignant lymphomas classified as centroblastic-centrocytic are follicular in 77%, follicular and diffuse in 20%, and diffuse in only 3%. Lennert also states that he disagrees with Dorfman (16), who emphasized that a nodular pattern has clinical significance. Both Lennert and Lukes say that a nodular pattern is irrelevant to the prognosis of malignant lymphoma. Butler et al (17), when they reclassified lymphomas according to the Lukes-Collins classification, divided them into follicular and diffuse. They found that the 5-year survival rate of the cleaved follicular center cell tumors was 74% when they were follicular and 28% when they were diffuse. In the mixed-cell group, the respective figures were 50% and 19%. They concluded that pattern does make a difference.

Let us turn now to large-cell non-Hodgkin's lymphomas. Malignant lymphomas termed "histiocytic" in the Rappaport classification harbor, according to Lukes, a variety of tumors including those composed of large cleaved follicular center cells, large non-cleaved follicular center cells, B immunoblasts, T immunoblasts, histiocytes, and perhaps some of undefined type. Lennert calls 98% of large-cell lymphoid tumors immunoblastic (4), while Lukes seems to use this term for only a minority of these (3). As yet, we have no explanation for this discrepancy. Let me emphasize that, whatever one calls the "histiocytic" or large-cell lymphomas, they are entirely different from other lymphoid tumors with respect to natural history, organ involvement, and microscopic and gross pathology. As Jaffe has pointed out, they do not show the homing patterns exhibited by other lymphoid tumors. DeVita and associates (18) clearly showed a plateau in the survival curve of advanced diffuse "histiocytic" lymphoma, which suggests that once the recurrence-free interval is long enough, the patient is probably cured. That is to say, after that point patients no longer die from "histiocytic" lymphoma, while losses by death from lymphocytic lymphoma continue even though the mean survival may be longer.

I would like to invite Dr. Lukes to clarify the clinical significance of the term "undefined," which, as he has already explained, means "lymphomas without markers." This must be a heterogeneous group, because Brouet et al (5) have already shown that when they studied surface markers of "histiocytic" lymphoma cells and reviewed similar studies from the literature, approximately 40% had no markers. Thus, many a tumor which we or Dorfman would include under "histiocytic" or "large lymphoid" respectively would be called "undefined" under the Lukes and Collins classification using criteria other than morphologic ones. Moreover, the term "undefined" may also include some lymphoblastic and undifferentiated lymphomas, creating another heterogeneous group of tumors of uncertain natural history, clinical behavior, and prognosis.

The term "immunoblastic" will enter the nomenclature and perhaps nothing is going to stop it. This term does not appear readily acceptable to all investigators. For instance, Brouet and associates (5) believe that in view of the present uncertainties concerning the exact maturational stages reached by the large cells along the pathways of differentiation toward B- or T-cell lines, a new classification of the "histiocytic" lymphomas appears premature, and that designations such as "immunoblastic sarcoma" do not really solve the problem because, in most instances, they are based chiefly on morphologic similarities that have been misleading in the past.

Cottier, Turk, and Sobin (19), who wrote a proposal for the World Health Organization, stated that "... care has been taken to use terms that are descriptive rather than those based on as yet debatable functional interpretations. Thus the term 'paracortical area' has been used in preference to 'thymus dependent area' and the term 'large lymphoid cell' in preference to 'immunoblast,' 'plasmablast,' etc."

A histologic classification should be clinically useful, scientifically accurate, reproducible, and easily taught and readily learned. What do we do now? We cannot wait until the NCI-supported large-scale retrospective study is finished; we have to classify cases now. I have continued to use the classification currently referred to as the "Rappaport classification," although I am uncomfortable with the term "histiocytic." I have modified our classification slightly and made some additions. I have accepted the suggestion of Butler et al (17), who divide the nodular lymphomas into lymphocytic, poorly differentiated, and mixed and no longer use the term "mixed histiocytic-lymphocytic." If anyone would like to replace "histiocytic" with "large cell," I will support the idea. Butler divides the diffuse lymphomas into well-differentiated and poorly differentiated lymphocytic, mixed cell, histiocytic, and undifferentiated; this is reasonable, but it is not sufficient in the light of present-day knowledge. We therefore suggest that four new categories be added, namely (*a*) malignant lymphoma-lymphoblastic; (*b*) Burkitt's lymphoma; (*c*) mycosis fungoides; and (*d*) malignant lymphoma-immunoblastic. As mentioned earlier, the

group of malignant lymphoma-lymphoblastic was previously included among undifferentiated or poorly differentiated lymphocytic lymphomas; the neoplastic cells resemble those of acute lymphoblastic leukemia and show pronounced mitotic activity. Burkitt's lymphoma, previously included among the undifferentiated lymphomas, is now recognized as a B-cell lymphoma (20) with distinctive clinicopathologic features and a characteristic response to therapy, at least in the African cases. Mycosis fungoides is a malignant lymphoma of T lymphocytes (21) which always originates in the skin and often spreads to lymph nodes and other internal organs. As for the immunoblastic lymphoma, we employ this term tentatively for lymphomas which are composed of large lymphoid cells with plasmacytoid features, and which arise in a pre-existing immunoproliferative process, such as Sjogren's syndrome, angioimmunoblastic lymphadenopathy, α-chain disease, and macroglobulinemia of Waldenstrom, or in immunosuppressed patients. We still have misgivings about the term "immunoblastic," but we do not know of a better one.

Dr. Lukes: I want to thank Dr. Rappaport for his discussion. He has raised too many points for me to cover in the allowed time, but I will try to respond to some major ones.

The classification we published contained a parenthesized chronic lymphocytic leukemia after small lymphocyte. It was put there to make it clear that this is a type of proliferation which may commonly end in chronic lymphocytic leukemia. I've always thought that this lymphocyte may be associated with chronic lymphocytic leukemia. I think we have always been in agreement on this point.

The undefined-cell (U-cell) type we set aside as a theoretic group. We need a category for cells which we cannot identify with techniques presently available. We have studied the Royal Marsden Cancer Hospital series and in the U-cell group we found six cases without convolutions, and none had mediastinal masses. Morphologically, convolutions were lacking in this group even though I thought the U-cell type was probably closely related to the convoluted type. The U-cell cases had all the other cytologic features—primitive chromatin, numerous mitoses, perinodal infiltration, and scanty cytoplasm, but round nuclei without convolutions. On the other hand, five of ten in the convoluted group of the same study had mediastinal masses, and hence the convoluted and non-convoluted groups though similar were different in their clinical presentations. At that time we also thought that the primitive-appearing round cells of non-convoluted type were probably an expression of a non-T-cell type of acute lymphocytic leukemia. We believe that the convoluted lymphocyte is the morphologic expression of T-cell acute lymphocytic leukemia; in some cases they have a mediastinal mass or enlarged nodes and in some cases they only have diffuse marrow involvement. The dramatic ones have mediastinal masses but we believe they are all biologically related.

The case Dr. Rappaport mentioned with a mixed proliferation of large and small T-cells fits well with the T-cell immunoblastic sarcoma—it usually shows a range of transformed lymphocytes.

We appreciate that proliferations of follicular center cells can appear in various forms (follicular, diffuse, and follicular and diffuse). If you look at the survival of patients with small cleaved follicular center cell disease, it is the same whether the pattern is diffuse or not. In looking at a single section, we saw a full range of numbers of follicles and the survival was the same whether there were follicles throughout, or in part of it, or none at all. The small cleaved cell has the capacity to form follicles, and biologically it is not an aggressive cell.

Dr. Rappaport said he was reluctant to use the term "immunoblastic," but I guess he finally succumbed to its attractions. We used the term "immunoblastic sarcoma" because we were certain that they were transformed lymphocytes. We knew they were going to be T-cell or B-cell in type. Therefore, we needed only one term to which we could add T-cell or B-cell later, so that's why we used the term immunoblastic sarcoma. We avoided using the words "malignant lymphoma-immunoblastic" because there are immunoblastic reactions.

Dr. Seligmann, I believe you discussed the validity of the word "immunoblastic" in the terminology of these tumors. Would you care to comment?

Dr. Seligmann: I understood Dr. Lukes to say that he called these cells and these lymphomas immunoblastic because they were of lymphoid origin and he wanted a general term to which he could add B or T later. He called them "immunoblastic," just as Dr. Dorfman would call them "large lymphoid cells" in order to say something different than "histiocytic." If this is the case, I see no reason to call them all immunoblastic; in Europe many pathologists using the Kiel classification call almost all large lymphoid cells "immunoblastic." Concerning large-cell lymphomas, we know that very few are composed of histiocytes but we have strong reasons for believing that this group is a heterogeneous one. The real problem is knowing what is in this category, and calling them all "immunoblastic" doesn't solve the problem. We

want the new classification to be clinically significant, scientifically accurate, and also reproducible. We heard this morning that, as far as cell type is concerned, pathologists in the Southwest Oncology Group studies achieved only a 60% reproducibility. Now, if we add too many new cell types, such as large non-cleaved, immunoblastic, and so on, reproducibility among American pathologists will fall to a level lower than that in countries where pathologists have less training in hematopathology. Dr. Lukes, how do you distinguish between the various large-cell types, especially "large non-cleaved" cells, "large transformed" cells, and "immunoblastic" cells?

Dr. Lukes: Reproducibility requires material that is well processed and cut so that pathologists can see the cells. As a morphologist, I can state that when we see a large cell that has the features of a transformed lymphocyte and it appears in a lymphoma that has a follicular pattern, we have a right to say that these are "follicular center cells" or "transformed" cells. Now, in addition, they often tend to be smaller and to have less cytoplasm, but they are still pyroninophilic. The cells of those diffuse lymphomas which we call "immunoblastic" tend to be larger, to have more cytoplasm, and to be more pyroninophilic. They may well show plasmacytoid features: there will be more cytoplasm and the nucleus will be eccentric, although the nucleus may still look like a transformed lymphocyte. In some proliferations, whether they be follicular or diffuse, you may see cytologic evidence of their follicular origin, namely, cleaved cells. The cleaved cell is a marker, which I believe provides reliable evidence of a follicular center cell proliferation. The large cells I am concerned about but the cleaved cells look the same on electron microscopy in both nodular lymphomas and normal follicles, so these two are closely related. The "histiocytic" group of Rappaport's system is not just immunoblastic sarcoma of the Kiel group classification or our classification. It also includes large cleaved follicular center cells, large non-cleaved follicular center cells, large transformed lymphocytes of B type, large transformed cells of T type, and also those few that may be true histiocytes. We hope to demonstrate that biologically these different large cells behave differently in response to therapy and that these differences are important. They may all have IgM on the surface but morphologically they look different and in the final analysis the important distinctions are going to be morphologic. Pathologists who have well-prepared sections and imprints, that is, good morphologic material, can learn how to make these distinctions.

Dr. Berard: Dr. Bloomfield, Dr. Rappaport pointed out that patients with tumors classified as diffuse "histiocytic" have shown an improved survival with intensive combination chemotherapy. These tumors are a unique group and, even though both they and the diffuse poorly differentiated lymphocytic group may be largely lymphoid, there does seem to be a difference in their survival curves. Would you care to comment?

Dr. Bloomfield: Dr. Rappaport raised an important point which I hope a combined classification supplemented by surface markers will be able to clarify. The patients with histiocytic lymphoma who have had this prolonged survival have been reported by the NCI group primarily, and more recently by groups at the University of Chicago and at Yale University. However, those cases make up only 25%–30% of patients with histiocytic lymphoma. I don't know how to mark those patients. The data I presented at this symposium included ten patients with diffuse histiocytic lymphoma, but it is not clear whether those who are still living will be long-term survivors. It's also possible that improved survival relates to sensitivity to drugs; our patients were treated with cyclophosphamide, vincristine, and prednisone (CVP). For certain kinds of tumors, these are not good drugs, and some of the other modes of therapy may be necessary to achieve survival in this group. I hope we will be able to answer that question as more people treat patients with histiocytic lymphoma, mark them, and then look at the various drugs. It is important to select out those modes of therapy that give long-term survival.

Dr. Berard: The patients at the University of Minnesota with "histiocytic" lymphomas were treated with CVP; those at the NCI received a four-drug combination similar to MOPP[3] or a newer five-drug combination. It may be that with similar therapy you would have had very much the same experience as the NCI group.

Dr. Jaffe, would you make some comment about the T and B maturational series, as depicted in your schema of lymphocyte differentiation? Dr. Rappaport raised a question about the relationship of an immunoblast to a plasmacytoid lymphocyte or a plasma cell.

Dr. Jaffe: In a diagram shown during my presentation at this symposium there was an immunoblast followed by an arrow leading to a plasma cell, and Dr. Rappaport asked whether I believe that a plasma cell follows an immunoblast in B-cell differentiation. This schema was not meant to illustrate all of the steps in the differentiation process of

[3] MOPP = mechlorethamine, vincristine (Oncovin), prednisone, and procarbazine.

either T or B lymphocytes, but was intended to make two points: first, that cells which are of the same origin (either B or T) can exhibit different morphologic expressions; second, that cells which are morphologically identical can be functionally heterogeneous (ie, either B or T). I did not intend to imply that plasma cells follow immunoblasts. In fact, there are multiple steps in the B-cell differentiation process, not all of which are completely understood, and we also believe that the small lymphocytes of well-differentiated lymphocytic lymphoma are closely related to plasmacytoid cells.

Dr. Berard: Let us now answer questions submitted in written form by the audience. *Dr. Dorfman: Most diagnoses are predicted on only one lymph node biopsy. What is the consistency in multiple-site biopsies in patients with non-Hodgkin's lymphoma? What evidence is there that multiple node biopsies at presentation are the same, for example, that all three nodes, inguinal, axillary, and cervical, would all be either nodular or diffuse?*

Dr. Dorfman: In a study that Dr. Kim and I published from Stanford some years ago, there was consistency of both architecture and cytology in 84% of 84 patients with non-Hodgkin's lymphomas subjected to surgical staging procedures (22). A patient is rarely subjected to lymph node biopsies from multiple peripheral sites, so the initial diagnosis in these patients was made from a cervical, an axillary, or an inguinal lymph node. They were then subjected to staging laparotomy, and the lesions in the spleen, para-aortic lymph nodes, etc, were consistent with the original lymph nodes in 84% of the cases. A similar consistency might be encountered in multiple peripheral sites.

Dr. Berard: *Dr. Lukes, what is the evidence that non-cleaved cells are dividing cells?*

Dr. Lukes: The evidence is indirect. Normal follicles contain many large non-cleaved cells or, as we prefer to call them, "transformed" cells. Furthermore, the frequency of mitoses is directly related to the frequency of large cells.

Dr. Berard: *Dr. Seligmann: Within non-Hodgkin's lymphomas, does one cell type convert to another, for example, poorly differentiated lymphocytic to histiocytic? If so, what are the T- and B-cell typings? Do they stay the same on repeated analysis?*

Dr. Seligmann: We don't have much experience with sequential studies of markers in individual patients. However, it appears from previous studies that patients who previously had a follicular-type lymphoma and then developed a large-cell ("immunoblastic") lymphoma had markers on the large cells that were the same as those of the previous follicular lymphoma. The nature (heavy chain class and light chain type) of immunoglobulin on the membrane of these large cells was the same as had been previously found on the follicular lymphoma cells. We found the same consistency when acute malignant transformation and large-cell malignant lymphoma supervene on previous chronic lymphocytic leukemia or macroglobulinemia.

Dr. Berard: *Dr. Byrne: With regard to malignant histiocytosis or histiocytic medullary reticulosis, is phagocytosis required for the diagnosis of this disease? Do you believe that malignant histiocytosis belongs in any classification of non-Hodgkin's lymphomas or should it be separated as a systemic proliferation?*

Dr. Byrne: To establish this diagnosis reproducibly, we insist that phagocytosis be demonstrated by cells that are cytologically abnormal. We differ from previous workers in that we accept phagocytosis of anything, not just erythrophagocytosis as had been reported by Robb-Smith. It is important that the cells be able to ingest and that the ingesting cells be cytologically abnormal. Therefore, I would require phagocytosis in order to establish a firm diagnosis. Next, I don't think that this disease belongs in any classification of non-Hodgkin's lymphomas. It is a systemic disease, perhaps comparable to a histiocytic leukemia.

Dr. Berard: We have learned that lymphoblastic tumors have a distinctive chromatin pattern, whether or not they have the nuclear convolutions described by Dr. Lukes. It's also been observed that the immunologic markers on these cells, although not present in all such tumors, are consistently those associated with T-cells. Furthermore, as Dr. Jaffe has shown at this symposium, when analyzed biochemically these cells have terminal deoxynucleotidyl transferase. Dr. Shaw has observed an interesting case which suggests that immunologically these tumors may be more heterogeneous than previously anticipated, even though the group is morphologically and clinically homogeneous.

Dr. Michael Shaw: A 16-year-old boy had what at first appeared to be acute lymphocytic leukemia with a mediastinal mass. Immunologic study showed that the patient had an immunoglobulin spike which turned out to be IgG, and there was monoclonal IgG on his blast cells. He also had in his blast cells an intermediate level of terminal deoxynucleotidyl transferase, which has to my knowledge been described only in the T-cells or null cells of acute lymphocytic leukemia. I would like to ask Dr. Lukes to explain this.

Dr. Lukes: We didn't say that all mediastinal masses were going to contain T-cells; indeed, we now have several tumors with surface markers that are of B-cell type. In our study at the Chil-

dren's Hospital of Los Angeles, although we encountered a large number that were of the convoluted type, several looked like transformed lymphocytes. These tumors, and those we did functional studies on, had cytoplasm and pyroninophilia, so morphologically they were distinguishable from the convoluted group.

Dr. Berard: Dr. Lukes, do we understand you to say that they were mediastinal lymphoblastic lymphomas?

Dr. Lukes: No, they are Burkitt-like. They are composed of round, rather regular, medium-sized cells with cytoplasm, strong pyroninophilia, and nucleoli. Morphologically they are distinguishable from lymphoblastic lymphomas, but they have mediastinal masses and some of them can be leukemic. These I believe are what Mathé called immunoblastic leukemia.

Dr. Berard: Dr. Shaw's case raises a different question. If you look at patients with acute nonmyelogenous leukemia, you will find that a small group, < 5%, have leukemia composed of cells morphologically identical to Burkitt cells, and those which look like Burkitt cells have B-cell markers. The other 95% are either null cells (65%–70%) or T-cells (25%–30%). Also, Burkitt's lymphoma occasionally occurs in the thorax. However, the 5% with B-cell markers do not have terminal deoxynucleotidyl transferase, at least to my knowledge. Concerning Dr. Shaw's case, I know of no precedent for a tumor presenting in the mediastinum with terminal deoxynucleotidyl transferase and monoclonal surface IgG. I would like Dr. Seligmann to comment.

Dr. Seligmann: Because until very recently we have not performed systematic studies of terminal deoxynucleotidyl transferase I have nothing to add, except that we have to be sure that the monoclonal IgG in this case was an actual product of the blast cells.

Dr. Berard: As new methods are introduced, for example, the assay for terminal deoxynucleotidyl transferase which is done in relatively few laboratories, we may find that the heterogeneity expressed by neoplastic cells will produce overlaps in immunologic or functional classifications. Perhaps we should not hastily assign such cells to the T lymphocytic or B lymphocytic series when their clinical and morphologic homogeneity may be the most important consideration.

Dr. Jaffe: Dr. Lukes, your classification is based on immunologic characteristics and it defines a cell as either a B-, T-, or null (undefined) cell. The series of convoluted or lymphoblastic lymphomas we recently reported (23) was clinically and morphologically homogeneous. I would consider them a homogeneous group, yet in half of them the cells were null cells by our techniques and yours. Would you put those tumors in your undefined group, or would you call them convoluted lymphocytic, recognizing that there was no way in which we could identify them to be of T-cell origin?

Dr. Lukes: All I can say is that we classify cases by our morphologic parameters, which include cytochemical ones, and then we look at the markers. In our experience they have markers of T-cells when we think they are convoluted.

Dr. Berard: Dr. Lukes, you rely heavily on morphology, do you not? In your presentation you showed us 59 cases, of which only one had been studied immunologically. Isn't that what you said?

Dr. Lukes: No. All 59 had been studied immunologically.

Dr. Berard: You also showed a retrospective series this morning.

Dr. Lukes: Yes. In the retrospective studies, only one had been studied. Those were based solely on morphology.

Dr. Berard: Exactly. If you assign cases to T lymphocytic or B lymphocytic categories in a retrospective study, you must be using only morphology.

Dr. Lukes: Yes. Morphology is basic to both our prospective and our retrospective studies.

Dr. Seligmann: Concerning cases with the clinical and morphologic presentation of convoluted lymphoblastic lymphoma but in which no markers are found, it may be crucial to determine whether these cells carry some T-cell antigens. We can demonstrate that in a few cases of T-derived acute lymphocytic leukemia, and in a few cases of Sézary syndrome, the cells don't form good E rosettes but are killed or labeled by antisera to T-cells. Thus we cannot answer Dr. Berard's question without gathering data with anti-T antisera. These cases may be T-derived but they could also be the lymphoma equivalent of the non-T, non-B acute lymphocytic leukemia. With respect to non-T, non-B acute lymphocytic leukemia, we must be extremely careful. When we look at these cases of acute lymphocytic leukemia without B or T surface markers, we find that they have terminal deoxynucleotidyl transferase, which is a thymic T-cell marker. However, evidence obtained using anti-Ia antisera suggests that they carry the so-called B-cell type of antigens. Now, it is known that anti-Ia will demonstrate these antigens on many kinds of leukemic cells, even myeloblasts, so I believe that the terminal deoxynucleotidyl transferase provides stronger evidence than the Ia type of antigen. Thus, when you increase the number of techniques and draw conclusions too rapidly, you encounter conflicting results, and the simultaneous presence in or on a neoplastic cell of markers of normal B- and T-cells may mean

that the "target" cell for the neoplastic event was a stem cell.

Dr. Berard: *Dr. Dorfman: We know that at Stanford cases were called "nodular" which were nodular in any focus but how do you classify lymphomas that are nodular versus those that are nodular and diffuse versus those that are diffuse?*

Dr. Dorfman: Before I answer that question, I would like to comment on the better prognosis that nodular lymphomas seem to have compared to diffuse lymphomas. The best evidence comes from a carefully controlled study done at Stanford by Jones and his colleagues. The pathologists reviewed these slides "blind." The results were given to the statistician and fed into a computer. It was a carefully controlled actuarial study. Similar studies were done at the NCI and at the University of Minnesota, and in fact half a dozen studies were presented at the Non-Hodgkin's Symposium in London in 1973 indicating that lymphomas with a nodular pattern have a better prognosis than those with a diffuse pattern. Contrary statements can be accepted only if they are based on studies performed with the same care as those already published.

As to the significance of the degree of nodularity, when we performed our study with Jones et al we arbitrarily chose to call nodular lymphomas "nodular" whether the nodes showed a uniform or a partial nodularity. The propriety of this decision was in some doubt until recently when Warnke, Kim, and Fuks reviewed 126 cases of nodular lymphoma (24). Their results indicated a progression from a follicular to a diffuse pattern. Some lymphomas show a focal nodularity in one area and a diffuse pattern elsewhere. In some cases the peripheral rim of the lymph node may show a nodular pattern while the bulk of the node shows a diffuse pattern. Of the 126 cases, 62 were of the poorly differentiated lymphocytic type in the Rappaport classification. Of these 62, 43 were completely nodular, 11 were predominantly nodular but focally diffuse, and eight were focally nodular but predominantly diffuse. They found that, when the information was put into the computer, the overall and disease-free survivals were the same in all three groups. Further, all three groups showed a statistically better survival than poorly differentiated lymphocytic lymphomas with a totally diffuse pattern. The mixed-cell type of nodular lymphoma (47 cases) showed the same phenomenon: overall and disease-free survivals were identical in the completely nodular and the focally nodular groups. Only in the small group of nodular "histiocytic" lymphomas (17 cases) were there statistical differences in overall survival and disease-free survival between lymphomas which were completely nodular and those which had only a focal nodularity. In our experience nodular lymphomas of large cell type are in fact usually associated with diffuse areas. The large cells seem to have a great tendency to proliferate; they are associated with more evidence of mitotic activity and it is these lesions that seem to progress to a diffuse pattern. It is not surprising, therefore, that we should have found this difference in survival. This study has shown that it is valid to call the majority of nodular lymphomas, ie, those of poorly differentiated lymphocytic type or mixed cell type, nodular even though the nodularity is only focal.

Dr. Berard: I think Dr. Lukes believes that a nodular pattern has no bearing on prognosis. Dr. Lukes, what hard data do you have to support this statement.

Dr. Lukes: Hopefully, the data from the Royal Marsden Cancer Hospital that Dr. Berard has asked for will be published soon. We did a study similar to Dr. Dorfman's and added to it a totally diffuse group. We separated 150 lymphomas into small cleaved and large cleaved, subdivided the follicularity of each into varying degrees, and identified 26 small cleaved cases that were entirely diffuse. Survival of these 26 diffuse small cleaved cases was the same as that of cases with a follicular pattern. My point is that survival relates to the cell type. These small cleaved cells usually make follicles but they do not always do so. In our diffuse cases, follicles were not present in the sections we had, but the survival was nevertheless the same.

Dr. Dorfman: I will be prepared to accept your data after you have submitted them to a statistician for analysis as we did at Stanford. May I add a practical point? Since everybody agrees that the presence of nodules, even a few nodules, is a marker of follicular lymphoma, we should hold on to that. We should keep the basic separation of nodular (or follicular) versus diffuse, because it is easier for a pathologist to make the distinction of nodular versus diffuse than to look for cleaved cells or B-cell markers. I am not saying that we should use the Rappaport classification and nothing else; in the near future we will have to make some changes. Rappaport himself has added new elements to his previous classification and he is right. However, I feel strongly that we should keep the distinction between nodular versus diffuse patterns because it is a clear marker.

Dr. Berard: *Dr. Lukes: Has your study been published?*

Dr. Lukes: No, not yet. I will submit it shortly.

Dr. Berard: *Dr. Dorfman: Do you know of any microscopic observations that would enable us, when confronted with a nodular lymphoma, to predict*

conversion to a diffuse lymphoma, since nodular lymphomas can progress to a diffuse form?

Dr. Dorfman: In our experience, nodular lymphomas of large-cell type are very frequently associated with diffuse areas, which suggests to me that these lymphomas have a higher risk of progression to a diffuse pattern. This conclusion seems warranted, because they have a greater degree of mitotic activity than nodular lymphomas of small-cell type; apparently these cells are proliferating and have a greater tendency to progress to a diffuse pattern.

Dr. Lukes: This is a principle we need to pursue. We need to take multiple biopsies from different peripheral sites in order to characterize the process which underlies the drift from nodular to diffuse. We also need sequential biopsies, particularly at relapse.

Dr. Berard: *Drs. Rappaport and Lukes: Pathologists can recognize nodularity in these tumors with a high degree of agreement, but, when you introduce such criteria as convolutions and cleavages, it becomes more difficult for pathologists to agree reproducibly. Can you delineate the differences between a cleaved cell, a convoluted cell, and the cerebriform cell of Sézary syndrome?*

Dr. Lukes: The pathologist has a real advantage because these distinctions are made more easily in good histologic sections than they are in smears. In a smear the cells are flattened out and are much more distorted, so the hematologist looking at a smear has that disadvantage.

In a one-cell-thick section there are many differences between these three types of cells. First, the cleaved cell is like a small lymphocyte. It has compact chromatin and a small amount of cytoplasm, and it looks inactive. It doesn't look primitive. Mitoses are infrequent. You see angulations, as Dr. Rappaport mentioned, and there may be irregular cells. Some of them show a single linear subdivision of the nucleus. By comparison, the convoluted cell is quite different because of its primitive, finely distributed chromatin. My colleague Dr. John Parker says he can recognize the chromatin of a convoluted cell on electron microscopy without seeing the nuclear configuration. Mitoses are numerous. The cell size varies from one to four or five lymphocyte nuclear diameters, quite different from the small cleaved cell. There may be five to seven mitoses per high magnification field, again totally different from the small cleaved cell. The cytoplasm is usually indiscernible and there may be no MGP positive cytoplasmic rim around the nucleus. The nucleus may be round with lines in it, almost like the side of a human brain. The configuration is often regular, but at times the nucleus appears almost lobulated. The Sézary cell is also quite different. It's much like the small lymphocyte and it may be difficult to recognize simply because good sections are needed to see linear subdivisions in the nucleus. Often these are clearly discernible only with an oil immersion (100 ×, objective).

Dr. Rappaport: The problem rarely poses itself because we are dealing with three unrelated conditions which cannot be readily confused. In the nodular lymphocytic lymphomas and their diffuse counterparts, we are dealing with tumors composed of relatively mature cells, ie, the indented or "cleaved" ones, and mitoses are usually scarce. In the so-called convoluted cell lymphomas, the lymphoid cells are immature and mitoses are abundant; and in mycosis fungoides the histologic picture is distinctive. These three types of lymphomas occur under such different clinical circumstances that the probability of any confusion is remote. Cell by cell it might be difficult to distinguish the convoluted nuclei of lymphoblastic lymphoma from the cerebriform nuclei of mycosis fungoides. Usually, however, some of the latter exhibit an extreme of nuclear infolding that is hardly ever seen in convoluted cells.

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Chemotherapy of the Non-Hodgkin's Lymphomas: The Stanford Experience[1]

Carol S. Portlock* and Saul A. Rosenberg[2,3]

SUMMARY

The Stanford University chemotherapy experience in the non-Hodgkin's lymphomas includes a prospective randomized trial in patients with stage IV disease and favorable histologies (nodular well-differentiated lymphocytic, nodular poorly differentiated lymphocytic, nodular mixed, and diffuse well-differentiated lymphocytic lymphoma) comparing combination chemotherapy with cyclophosphamide, vincristine, and prednisone (CVP) vs split-course CVP and total lymphoid irradiation vs single alkylating-agent therapy. No significant differences have been noted among 63 patients in the three treatment groups in terms of complete remission rate, disease-free survival, and survival. Also presented is a retrospective review of 35 previously untreated patients with favorable histologies who, because of advanced but not threatening disease, were initially left untreated and followed until systemic symptoms or local disease progression required treatment. This occurred in half of the patients within the first 3 years; others are untreated for periods up to 10 years, and 70% are alive at 6 years. In the unfavorable histologies (diffuse histiocytic lymphoma, diffuse mixed lymphoma, and nodular histiocytic lymphoma), combination chemotherapy with cytosine arabinoside, adriamycin, and 6-thioguanine is reported in 61 patients. The overall response rate for all patients is 54.1%, and the complete response rate in 18 previously untreated patients is 44.4%. For complete responders the median disease-free survival is 29 months, and 80% are still alive at 1 year.

[Cancer Treat Rep 61:1049–1055, 1977]

When studying the treatment of the non-Hodgkin's lymphomas, three methods are commonly used: the prospectively randomized clinical trial, the application of new modes of therapy or new drug combinations in a non-randomized prospective trial, and the retrospective analysis of a given treatment program. In the following discussion, data from each of these methods will be used to illustrate the therapy of the non-Hodgkin's lymphomas at Stanford University.

The non-Hodgkin's lymphomas comprise a broad spectrum of lymphoid malignancies with differing clinical presentations, histopathologies, responses to treatment, and prognoses. In order to treat this diversity of diseases, five prospective randomized clinical trials are in progress at Stanford Medical Center, each of which has two or three treatment options.

ADVANCED NON-HODGKIN'S LYMPHOMAS WITH FAVORABLE HISTOLOGIES: PROSPECTIVE TRIAL

The J-6 study, which was initiated in July 1971 and closed in October 1974, was designed to study three treatment programs for patients with stage IV non-Hodgkin's lymphomas with favorable histologies—those with well-differentiated lymphocytic lymphomas of the nodular (NLWD) or diffuse (DLWD) type, those with nodular poorly differen-

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tiated lymphocytic lymphoma (NLPD), and those with nodular mixed lymphocytic and histiocytic lymphoma (NML). The preliminary results of this trial were reported earlier (1), and this paper presents a maximum followup of 59 months with a median of 33 months for all patients.

Materials and Methods

Previous reports provided details of the study (1–3), histopathologic criteria (4), diagnostic methods (2,3), and staging designations (5). Sixty-three patients with previously untreated stage IV non-Hodgkin's lymphomas with favorable histologies (NLWD, NLPD, NML, and DLWD) were prospectively randomized to receive combination chemotherapy alone with cyclophosphamide, vincristine, and prednisone (CVP) (6),[4] or split-course CVP with total lymphoid irradiation (CVP-TLI), or continuous single alkylating-agent chemotherapy.

The characteristics of the patient population, the definitions of complete and partial response, and the statistical methods employed have been described elsewhere (1).

Treatment Results

Response to treatment has been excellent in all three treatment groups, with > 95% of all patients responding to therapy. Pathologically documented complete remissions have been seen in 82.6% of the CVP group, in 70% of the split-course (CVP-TLI) group, and in 65% of the single-agent group ($P > 0.2$) (table 1). Twelve complete responders have relapsed: six in the CVP group (one has died), five in the CVP-TLI group (one has died), and one in the single-agent group who is being followed without treatment. Partial responses have been seen in 17.4% of CVP patients, 25% of CVP-TLI patients, and 30% of single-agent therapy patients. Of the 15 partial responders, only one is currently receiving treatment; he is clinically free of disease but has not had a pathologically documented complete remission. The disease in the other 14 partial responders has progressed and five patients have died (one in the CVP group, three in the split-course group, and one in the single-agent group). There were only two nonresponders in the entire study population; one in the split-course group died of disease after two cycles of CVP before receiving any radiation therapy, and one single-agent patient is alive with disease and is receiving combination chemotherapy.

TABLE 1.—Response to treatment: the J-6 study

	No. of patients (%)		
	Treatment		
Response	CVP	CVP-TLI	Single-agent
Complete	19 (82.6)	14 (70)	13 (65)
Partial	4 (17.4)	5 (25)	6 (30)
None	0	1 (5)	1 (5)
Total	23	20	20

With a maximal followup of 59 months and a median of 33 months for all patients, 28 patients have disease which has progressed after initial therapy. Looking at the actuarial time to disease

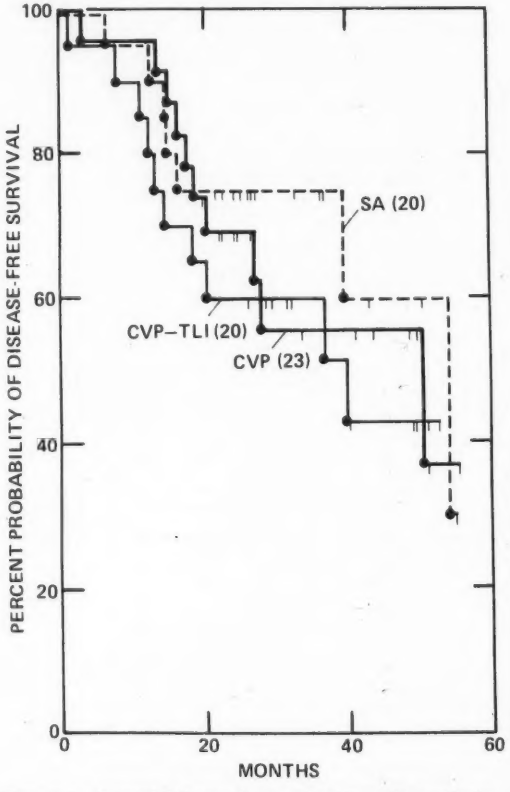

FIGURE 1.—Actuarial disease-free survival from date patients were first seen at Stanford to disease progression (J-6 study).

[4]Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate.

Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1).

Prednisone: NSC-10023; CAS reg. No. 53-03-2; pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-.

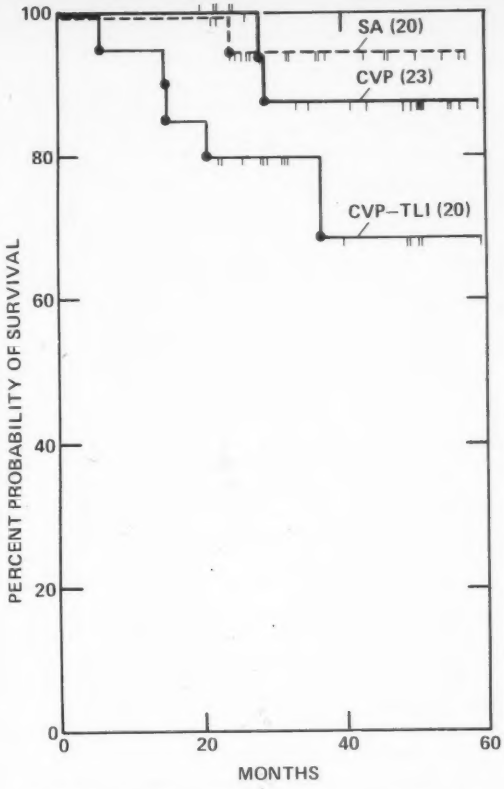

FIGURE 2.—Actuarial survival from date patients were first seen at Stanford (J-6 study).

progression from initiation of therapy, one can see that more than half the patients remain alive without evidence of disease progression at 35 months and that there are no significant differences between the three treatment groups in terms of disease-free survival ($P > 0.05$) (fig 1).

Similarly, there are no significant differences between the three treatment groups in terms of actuarial survival where the median survival has not been reached, and > 80% of all patients remain alive at 5 years ($P > 0.07$) (fig 2).

In general, the three treatment programs were well tolerated; the toxicities were those reported previously for CVP, TLI, and continuous single alkylating-agent therapy. Table 2 lists the significant toxic effects.

Although a longer period of followup will be needed to judge the relative efficacies and risks of the three treatment approaches, certain tentative conclusions can be made. *A.*—Each of the three

TABLE 2.—Toxic effects of treatment: the J–6 study

Toxic effect	No. of patients, Treatment: CVP (23)	CVP-TLI (20)	Single-agent (20)
Bacterial infections	3	3	2
Herpes zoster	1	2	1
Hemorrhagic cystitis	2	1	5
Hypothyroidism	—	1	—
Persistent cytopenia	—	5	1

treatment programs achieved an excellent response and produced prolonged disease-free survival in patients with stage IV non-Hodgkin's lymphomas with favorable histologies. *B.*—The combined approach of split-course CVP and high-dose TLI does not appear to improve the duration of complete remission compared to CVP alone, and makes salvage of partial responders difficult because of treatment-induced bone marrow hypoplasia. *C.*—Single-agent chemotherapy, given continuously, is capable of inducing pathologically documented complete remissions in these patients, and over the 5-year followup, single-agent therapy has been associated with overall survival as good as or better than that achieved with the more aggressive treatment programs.

ADVANCED NON-HODGKIN'S LYMPHOMAS WITH FAVORABLE HISTOLOGIES: RETROSPECTIVE REVIEW OF PATIENTS RECEIVING NO INITIAL THERAPY

Recognizing that the favorable non-Hodgkin's lymphomas have excellent prognoses with treatment, we examined the following question: is any initial treatment necessary if the patient is asymptomatic? Since 1960 the oncology division at Stanford has adopted the following practice: if a patient is not participating in protocol studies and has an advanced non-Hodgkin's lymphoma with favorable histopathology and is relatively asymptomatic without threatening disease, treatment may be withheld in order to evaluate the pace of disease and the necessity of treatment.

Materials and Methods

During the past 16 years, 35 patients with advanced non-Hodgkin's lymphomas who were previously untreated have been followed without initial

TABLE 3.—Characteristics of the patient population: favorable non-Hodgkin's lymphomas with no initial therapy

Characteristic	
Total No. of patients	35
Sex	
Women	16
Men	19
Age (yrs)	
Range	36–77
Mean	57.3
Histology	
NLWD	1
NLPD	13
NML	7
DLWD	6
DLID*	1
DLPD	7
Disease stage	
III	3
IV	32
Symptoms	
A	30
B	5

*DLID = diffuse lymphocytic intermediate differentiated.

therapy until such time as treatment became indicated. Table 3 describes the characteristics of this patient population. There were 16 women and 19 men ranging in age from 36 to 77 years (average, 57.3 years). At presentation, clinical disease was usually limited to lymph node involvement with or without splenomegaly. Only five patients had extranodal disease on clinical examination: three with skin, one with breast, and one with lung involvement. Bone marrow biopsy was positive in 30 of the 35 patients, and in only three was disease apparently limited to nodal sites (without confirmation through staging laparotomy). Only five patients had systemic symptoms, three with significant weight loss and two with night sweats. Table 3 describes the pathology; it is of interest that seven patients had diffuse poorly differentiated lymphocytic lymphoma.

TABLE 4.—Reasons for treatment: favorable non-Hodgkin's lymphomas with no initial therapy

Reason for treatment	No. of patients
Bulky adenopathy	15
Progressive skin disease	2
Progressive lung disease	1
Cord compression	1
Patient desired therapy	1

TABLE 5.—Initial treatments for progressive disease: favorable non-Hodgkin's lymphomas with no initial therapy

Treatment	No. of patients
Single alkylating agent	12
Combination chemotherapy	4
Local field radiation therapy	3
Whole body irradiation	1

Results

If one looks at the actuarial probability of requiring treatment from the time of diagnosis to the initiation of therapy, one can see that half the patients have received some kind of therapy by 3 years; however, there are still 16 patients who have not yet required treatment for periods of up to 10 years (fig 3). Therapy was usually initiated for progressive bulky lymphadenopathy (table 4), but was also given for progressive skin and lung disease and, in one instance, for early cord compression. The kinds of treatment utilized are listed in table 5.

The survival for this selected group has been excellent. Only five patients died during a followup of from 2 months to 12 years (median followup, 41 months), and > 70% of the patients are alive at 6 years (fig 3).

Even though these data represent a selected patient population, they do serve to emphasize that the prognosis for those patients with advanced non-Hodgkin's lymphomas with favorable histologies can be excellent even without initial therapy, and that prospective trials such as that described above must take these data into consideration when analyzing the influence of treatment on survival.

ADVANCED NON-HODGKIN'S LYMPHOMAS WITH UNFAVORABLE HISTOLOGIES: CAT[5] CHEMOTHERAPY

In contrast to the favorable non-Hodgkin's lymphomas discussed thus far, patients with advanced unfavorable histopathology—histiocytic lymphoma of the nodular (NHL) or diffuse (DHL) type and diffuse mixed lymphocytic and histiocytic lymphoma (DML)—have been reported to have very poor prog-

[5]CAT = cytosine arabinoside, adriamycin, and 6-thioguanine.
Cytosine arabinoside: NSC-63878; CAS reg. No. 69–74–9; cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride.
Adriamycin: NSC-123127; CAS reg. No. 23214–92–8.
6-Thioguanine: NSC-752; CAS reg. No. 1832–72–0; purine-6-thiol, 2-amino-.

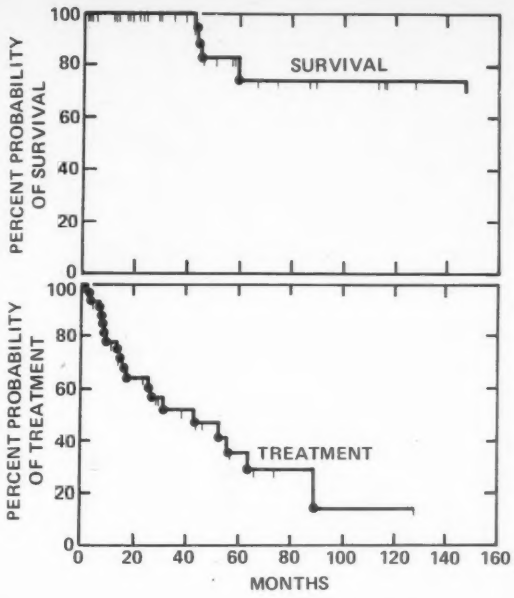

FIGURE 3.—Advanced non-Hodgkin's lymphomas with no initial therapy; actuarial survival from date of diagnosis and actuarial probability of requiring treatment from date of diagnosis to progression of disease.

noses even with treatment. However, the introduction of new aggressive drug combinations has altered the prognosis for these patients dramatically, and evidence is growing that some may in fact be cured of their disease (7,8).

At Stanford we have been studying CAT chemotherapy for the treatment of patients with advanced non-Hodgkin's lymphomas with unfavorable histologies.

Materials and Methods

Between October 1972 and August 1976, 61 consecutive unselected patients have received CAT at Stanford Medical Center. All biopsy specimens were reviewed at Stanford and classified according to the histopathologic criteria of Rappaport et al (4). Before chemotherapy was begun, patients were evaluated for extent of disease with routine physical examination, chest roentgenogram, bone marrow biopsy, and usually lymphography and/or iv pyelogram. Frequently, but not routinely, we obtained biopsy of other evident sites of extranodal involvement, including percutaneous liver biopsy. The extent of disease was staged according to the Ann Arbor classification (5).

The combination chemotherapy employed in all patients was cytosine arabinoside, 3 mg/kg iv on Days 2–5 in the morning; adriamycin, 60 mg/m² iv on Day 1; and 6-thioguanine, 2.5 mg/kg orally on Days 2–5, 12 hours after each dose of cytosine arabinoside. CAT was repeated every 3–4 weeks, depending upon blood cell counts (usually initiated when the wbc count was $> 4000/mm^3$ and the platelet count was $> 100,000/mm^3$) for a total of nine cycles (or approximately 500 mg/m² total dose of adriamycin). No maintenance chemotherapy was given.

The patient population is described in table 6. There were 18 women and 43 men whose average age was 52.2 years. Eighteen patients were previously untreated, 12 had relapsed after radiation therapy, ten had relapsed after chemotherapy, and 21 had relapsed after receiving both radiation and chemotherapy. In those previously untreated, disease was limited to lymph nodes in 11 patients and involved extranodal sites in seven patients.

No patients were excluded from the analysis because of drug toxicity, incomplete therapy, or insufficient data. Definitions of complete and partial response and the methods of statistical analysis have been presented elsewhere (9).

Results—Drug Dosage and Toxicity

In general, CAT was relatively well tolerated. The hematologic toxicity was manifested primarily by reversible leukopenia and thrombocytopenia

TABLE 6.—Characteristics of the patient population: CAT chemotherapy

Characteristic	
Total No. of patients	61
Sex	
Women	18
Men	43
Age (yrs)	
Range	16–85
Mean	52.2
Histology	
NLPD	2
NML	1
NHL	4
DLPD	3
DML	2
DHL	45
DUL*	4
Stage	
II	4
III	13
IV	44

*DUL = diffuse undifferentiated lymphoma.

TABLE 7.—Toxic effects of treatment: CAT chemotherapy

Toxic effect	No. of patients
Bacterial infections	13
Herpes zoster	1
Pneumocystis carinii	1
Thrombocytopenia requiring transfusion	4
Congestive heart failure	2

which were maximum at 10–14 days. The average wbc count nadir was 2000/mm^3 and the average platelet count nadir was 71,000/mm^3. The mean number of cycles given was five and > 80% of the calculated dose of each drug was administered to all patients. Other acceptable and reversible toxicities included nausea, vomiting, mucositis, and alopecia. Significant toxicities of treatment encountered in this study are listed in table 7.

Results—Chemotherapy

Overall, 54.1% of the patients responded to CAT and 16.4% obtained a pathologically documented complete remission at the conclusion of all therapy (table 8). However, if we look at response to CAT in terms of prior treatment, it can be seen that complete remissions were confined almost exclusively to those without prior therapy; 44.4% of these patients obtained a complete remission compared to 4.7% of those with prior treatment.

The disease-free survival for all patients following CAT is very short, a median of only 4 months, and is similar for previously treated and untreated patients. If, on the other hand, we look at the disease-free survival according to response to CAT, we see that complete responders have a significantly better disease-free survival compared to partial responders or nonresponders ($P < 0.04$) (fig 4). The median disease-free survival for complete responders is > 1 year compared to < 5 months for partial responders.

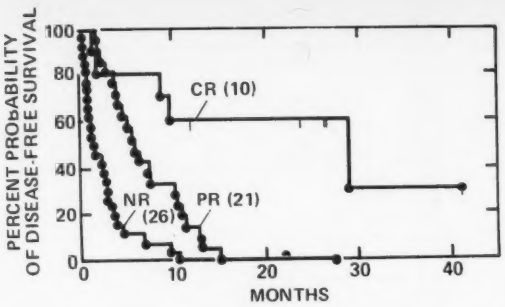

FIGURE 4.—Actuarial disease-free survival from initiation of CAT to progression of disease according to response to treatment.

Similarly, survival is also affected by response to treatment. The median survival for all patients is only 9.5 months, yet 80% of complete responders are alive at 1 year whereas less than half of the partial responders are still alive ($P < 0.05$) (fig 5).

Although the Stanford experience with CAT chemotherapy is comparable to other reports in terms of complete remission rate in previously untreated patients, this drug combination is disappointing because the complete remissions obtained are not as uniformly durable as those previously reported by DeVita et al (7) or Berd et al (8) using other drug combinations in previously untreated patients. We can only speculate whether maintenance therapy would have improved these results, yet maintenance was not utilized after complete remission with C-MOPP (7),[6] where remission duration was > 80% at 3 years. Because of our poor results with CAT chemotherapy, we are investigating other adriamycin-containing combinations and are modifying the dose schedule of CAT in an attempt to improve our complete remission rate and duration.

[6]C-MOPP = cyclophosphamide, vincristine, prednisone, and procarbazine.

TABLE 8.—Response to treatment: CAT chemotherapy

Response	No. of patients (%)		
	All patients (61)	Previously untreated (18)	Previously treated (43)
Overall	33 (54.1)	14 (77.8)	19 (44.2)
Complete	10 (16.4)	8 (44.4)	2 (4.7)
Partial	23 (37.7)	6 (33.3)	17 (39.5)
None	28 (45.9)	4 (22.2)	24 (55.8)

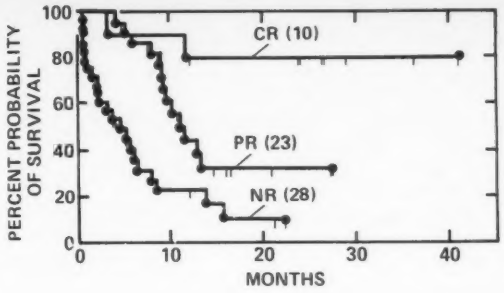

FIGURE 5.—Actuarial survival from date of initiation of CAT according to response to treatment.

The Stanford experience in advanced non-Hodgkin's lymphomas is as diverse as the diseases themselves. In the favorable lymphomas we have found that, in terms of complete remission rate, disease-free survival, and survival, single alkylating-agent therapy is as effective as more aggressive combination chemotherapy with CVP or combined modality therapy with CVP-TLI. We have also found that a highly favorable group of patients with advanced non-Hodgkin's lymphomas can be identified who are asymptomatic without threatening disease at presentation and can be left initially untreated until such time as their disease progresses. Half of these patients require some kind of therapy by 3 years, but some patients can be left untreated for as long as 10 years. The survival of these patients is excellent; > 70% are alive at 6 years. At the other end of the spectrum are the unfavorable lymphomas treated with an adriamycin-containing combination called CAT where 44% of previously untreated patients obtained a complete remission and 60% of complete responders are without evidence of disease progression at 1 year. Four of these patients have been disease-free from 2 to 3½ years, and as others have previously reported, such durable complete remissions may represent cure of an otherwise unfavorable lymphoma.

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Combination Chemotherapy in Non-Hodgkin's Lymphoma: Results of Long-Term Followup [1]

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SUMMARY

Combination chemotherapy can be effectively administered to patients with advanced non-Hodgkin's lymphoma. While patients with nodular lymphomas have been known to have a more favorable prognosis than patients with diffuse lymphoma, the response to combination chemotherapy in the "favorable" nodular lymphomas can be used to predict ultimate survival rates. Patients with nodular poorly differentiated lymphocytic lymphoma who achieve a complete remission with combination chemotherapy (67%) have a median survival of approximately 8 years compared to only 3 years for patients who fail to achieve a complete remission. Patients with nodular mixed lymphoma achieving a complete remission (77%) have not yet reached their median survival, compared to a median survival of only 13 months for patients failing to achieve a complete remission. Furthermore, in contrast to nodular poorly differentiated lymphocytic lymphoma patients (only 33% alive with no evidence of disease), patients with nodular mixed lymphoma who achieve a complete remission tend to remain disease free (79% alive with no evidence of disease). As previously reported, our data confirm that the achievement of a complete remission in diffuse lymphomas has prognostic significance. Median survival for diffuse histiocytic lymphoma patients who achieve a complete remission (47%) has not yet been reached, with 64% of patients still alive and free of disease, compared to only 7 months' median survival for partial responders. Only 32% of patients with diffuse poorly differentiated lymphocytic lymphoma achieved a complete remission; 67% are still alive, compared to a median survival of 10.4 months for partial responders. Nodular lymphoma patients tend to have a higher complete remission rate (71%) and, in the case of nodular mixed lymphoma, this remission appears to be durable. Diffuse histiocytic lymphoma patients with poor prognostic factors and diffuse poorly differentiated lymphocytic lymphoma patients must be considered for new therapeutic modalities. The ability to achieve a complete remission with intensive therapy conveys an improved prognosis in both "favorable" and unfavorable histologic subtypes.

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The malignant lymphomas rank sixth both in incidence and cause of death from malignancy in both men and women in the United States. It is estimated that 29,500 new cases will be diagnosed in 1976, and that 19,000 patients will die from these diseases during the year; 65% of these patients will have one of the several types of non-Hodgkin's lymphomas. As early as 1966, Rappaport (1) proposed a detailed histologic classification with prognostic significance, but it failed to receive rapid widespread acceptance. Finally, however, Jones et al (2) in 1972 and others (3,4) confirmed that the degree of cellular differentiation and the histologic

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architecture of the lymph nodes have profound prognostic implications. Important additions to our understanding of non-Hodgkin's lymphomas have resulted from the systematic, sequential staging procedures to identify otherwise occult dissemination of disease. Such studies have demonstrated that the majority of patients with non-Hodgkin's lymphomas have disseminated disease at presentation (5–8), and the recognition of the extent of this dissemination has led to new approaches in therapy.

Before physicians recognized the high incidence of dissemination, radiotherapy alone produced only a 10% long-term response rate, and most patients relapsed outside previously irradiated fields (9,10). Chemotherapy was considered palliative, and previous histologic classifications did not identify those patients who were likely to respond to either single agents or drug combinations. A systematic approach to therapy, based on a uniform histologic classification with prognostic significance and comprehensive staging techniques, has made possible the identification of effective forms of treatment for the non-Hodgkin's lymphomas. Long-term disease-free survival for many of these patients can now be achieved without continual chemotherapy. This report presents the results of combination chemotherapy in 199 patients treated at the Medicine Branch, Division of Cancer Treatment, National Cancer Institute, after detailed staging and uniform histologic classification had been completed.

MATERIALS AND METHODS

Histology

One hundred and ninety-nine patients with non-Hodgkin's lymphoma have completed combination chemotherapy programs between July 1, 1963, and August 31, 1976. The original biopsy specimens have been reviewed and reclassified into one of eight histologic classifications based on cell type, degree of cellular differentiation, and pattern of involvement, ie, nodular or diffuse (table 1). The only patients excluded from this report are those with diffuse undifferentiated lymphoma, Burkitt's type, and a small group of patients who received single-agent chemotherapy. Those patients in whom two distinct histologic subtypes coexist (< 6% of the total) were assigned to the subtype considered at that time to have the least favorable prognosis (ie, poorly differentiated over well differentiated, and diffuse over nodular). Finally, the Rappaport classification of lymphomas made no provision for lymphocytic lymphomas of intermediate differentiation; in this study, such patients were assigned to the poorly differentiated category. There were

TABLE 1.—Non-Hodgkin's lymphoma: histologic classification for 199 patients

Nodular	No.	%	Diffuse	No.	%
NWDL	0	0	DWDL	11	5.5
NPDL	49	24.5	DPDL	25	12.5
NML	31	15.5	DML	10	5
NHL	4	2	DHL	62	31
			DUL, pleomorphic	7	3.5
Total	84	42.5		115	57.5

slightly more patients with diffuse lymphomas (58%) than nodular (42%). The most common cell type in the nodular category was poorly differentiated lymphocytic lymphoma (NPDL),[3] which constituted 24.5% of this series. No cases were classified as nodular well-differentiated lymphocytic lymphoma. The most common cell type of the diffuse lymphomas was diffuse histiocytic—31% (table 1).

Staging

Staging procedures routinely included intravenous pyelography and/or lymphangiography, percutaneous bone marrow, and percutaneous liver biopsies. Since 1971, all patients have undergone more extensive staging, including radioisotopic liver, bone, and gallium scans, peritoneoscopy with multiple liver biopsies, and laparotomy if widespread disease could not be otherwise demonstrated. Details of this staging study have been published (5) and are presented elsewhere in this symposium (11). With rare exceptions, extranodal disease was confirmed by biopsy. The extent of disease is designated in terms of pathologic stage as outlined at the Ann Arbor conference (12). Seventy-four percent of patients were documented to have stage IV disease by these procedures. Twenty percent had stage III disease; 11 patients (6%) had stage I or II disease but had had recurrences within radiation fields following adequate radiotherapy.

Therapeutic Regimens

Three basic treatment programs were used. For lymphocytic lymphomas (NPDL, DPDL, DWDL) a cyclic combination regimen (CVP) consisting of cyclophosphamide (400 mg/m²/day for 5 days), vincristine (1.4 mg/m² on Day 1), and prednisone (100

[3] NPDL = nodular poorly differentiated lymphocytic lymphoma; DPDL = diffuse poorly differentiated lymphocytic lymphoma; DWDL = diffuse well-differentiated lymphocytic lymphoma; NHL = nodular histiocytic lymphoma; DHL = diffuse histiocytic lymphoma; NML = nodular mixed histiocytic-lymphocytic lymphoma; DML = diffuse mixed histiocytic-lymphocytic lymphoma; and DUL = diffuse undifferentiated lymphoma.

mg/m²/day for 5 days) was administered in 21-day cycles. Treatment details, including dose modifications, have been previously reported (13). If a complete remission (CR) was achieved with a minimum of four cycles of CVP, an additional two cycles of consolidation were administered. In those patients who failed to attain a clinical remission in four cycles of therapy, additional cycles of CVP were given until there was complete disappearance of disease, whereupon two consolidation cycles of therapy were given, or until regrowth of tumor occurred. No patients who achieved a CR received maintenance chemotherapy except for five who received two to five cycles of CVP in 1970–71 as part of a maintenance study which was subsequently discontinued.

The second treatment regimen was MOPP or C-MOPP. Early in the development of combination chemotherapy regimens, the MOPP combination utilized for Hodgkin's disease was also used for the non-Hodgkin's lymphomas; it consisted of mechlorethamine (6 mg/m² on Days 1 and 8), vincristine (1.4 mg/m² on Days 1 and 8), procarbazine (100 mg/m²/day on Days 1–14), and prednisone (40 mg/m² on Days 1–14). With the subsequent recognition that cyclophosphamide had a higher response rate as a single agent than mechlorethamine (14), it was substituted (at a dose of 650 mg/m² on Days 1 and 8) for mechlorethamine. These regimens were used in the treatment of patients with histiocytic (NHL, DHL), mixed histiocytic-lymphocytic (NML, DML), or undifferentiated (DUL) lymphomas.

The third basic treatment program was BACOP, which has been used since 1972 to treat patients with DHL or DML. This regimen consists of cyclophosphamide (650 mg/m² on Days 1 and 8), vincristine (1.4 mg/m² on Days 1 and 8), adriamycin (25 mg/m² on Days 1 and 8), bleomycin (5 units/m² on Days 15 and 22), and prednisone (60 mg/m² on Days 15–28) administered every 28 days. The original dose of bleomycin, 15 units/m², was decreased to 5 units/m² after significant pulmonary toxicity developed in four of the first 16 patients treated. Subsequent pulmonary toxicity with the lower bleomycin dose has been rare. Details of this regimen, including toxicity, dose modification, etc, have been published elsewhere (15).

In addition to the above regimens, ten patients received local radiotherapy concurrent with or just before chemotherapy, because of central nervous system involvement (three patients), extensive gastrointestinal involvement with impending perforation (three patients), or destructive bone lesions in weight-bearing areas (four patients).

All patients entered in a combination chemotherapy program are included. All began receiving therapy within 3 months of diagnosis. No patients are excluded because of toxicity, insufficient data, or incomplete therapy. Only two patients were lost to followup; for the purpose of this analysis, both were considered to have died at the time they were lost to followup. One month after completion of therapy, all patients who were clinically in CR were reevaluated for evidence of residual tumor by repeat staging procedures, including lymphangiography, bone marrow, and/or liver biopsies if the results of such tests were abnormal before therapy. The patient was declared to be in a true CR only after the above tests were performed and found to be negative. Patients discovered to have residual disease continued to receive therapy until a documented CR was achieved, the patient's disease clinically progressed, or toxicity supervened. A CR was defined as the complete disappearance of all previous disease, verified by appropriate restaging procedures, and a return to normal performance status. A partial remission (PR) was defined as a $\geq 75\%$ reduction in all evidence of disease lasting at least 1 month. Survival was calculated from the start of therapy. Remission duration was calculated from the last day of treatment to the first documentation of recurrent disease. The data were analyzed by the method of Kaplan and Meier (16) and life-table curves were compared by Gehan's generalized Wilcoxon test (17). Proportions were compared by the Fisher exact method (18).

Treatment Groups

The details of the various histologic subtypes, stages of disease, and forms of therapy are summarized as follows.

Diffuse well-differentiated lymphocytic lymphoma.—There were 11 patients with a median age of 55 years (range, 38–67). All were stage IV except one who was clinical stage III in 1963 but had no staging biopsies. Ten patients received conventional combination CVP; one patient received cyclophosphamide, vincristine, and procarbazine sequentially rather than simultaneously early in the development of chemotherapy regimens. One patient had received local radiotherapy because of an initial diagnosis of cholangiocarcinoma before referral. Two patients received maintenance therapy for four or five cycles following chemotherapy induction.

Diffuse poorly differentiated lymphocytic lymphoma.—These 25 patients had a median age of 50 years (range, 14–65). One patient was stage II, three were stage III, and 21 were stage IV. Two patients had previously received involved-field radiotherapy for originally localized disease, a

third patient did not respond to hemibody irradiation (HBI), and a fourth received radiotherapy to Waldeyer's ring during the initial staging workup. All patients received CVP chemotherapy.

Nodular poorly differentiated lymphocytic lymphoma.—These 49 patients had a median age of 48 years (range, 27–69). One patient was stage II, 12 were stage III (including five who were staged with or without a single bone marrow biopsy early in the development of the treatment program), and 36 were stage IV. One patient received C-MOPP; the other 48 received CVP. Three patients previously received radiotherapy (involved-field, two; HBI, one), including the only patient who was stage II. Further, two patients received an additional two to four cycles of therapy after each had achieved a CR.

Nodular mixed histiocytic-lymphocytic lymphoma.—These 31 patients had a median age of 49 years (range, 25–67). Two patients were stage II, six were stage III, and 23 were stage IV. Three patients had failed previous radiotherapy, including the two patients who were stage II. One patient received MOPP initially and was switched to C-MOPP upon re-interpretation of his biopsy. Six received CVP and one received BACOP because initially their biopsies were reported as another histologic type. Twenty-three received C-MOPP. One received maintenance CVP therapy after achieving a CR.

Diffuse mixed histiocytic-lymphocytic lymphoma.—These ten patients had a median age of 46 years (range, 41–62). Three patients were stage III and seven were stage IV. Four patients were treated with CVP, four with C-MOPP, and two with BACOP.

Nodular histiocytic lymphoma.—These four patients were 38, 40, 56, and 59 years of age. Two were stage III and two were stage IV. Three received C-MOPP; one received BACOP. Two had previously received total-body irradiation.

Diffuse histiocytic lymphoma.—These 62 patients had a median age of 49 years (range, 9–70). One patient was stage I, five were stage II, 13 were stage III, and 43 were stage IV. Thirteen patients had received previous radiotherapy and failed, including the one stage I patient and the five stage II patients; four patients had received previous chemotherapy. Seventeen patients were treated with C-MOPP, 34 with BACOP, five with MOPP, and five with CVP (because of initial classification as DPDL). In one patient methotrexate was substituted for procarbazine in the C-MOPP regimen early in the development of combination therapies.

Diffuse undifferentiated lymphoma.—These seven patients had a median age of 29 years (range, 21–61). One patient was stage II, one was stage III, and five were stage IV; the stage II patient had previously failed radiotherapy. Two patients were treated with C-MOPP and five with CVP.

RESULTS

Response Rates by Histologic Type (Table 2)

Diffuse well-differentiated lymphocytic lymphoma.—Seven of 11 patients (64%) with DWDL achieved a CR but five of the seven eventually relapsed; the median duration of remission was 23 months (range, 4–107+) (fig 1). The survival of CR patients ranged from 41 to 156+ months, with a median survival of 84 months (table 2) compared with survivals of 1, 5, 56+, and 81+ months for patients with PR (table 2). The median survival for the entire group of DWDL patients was 78.2 months.

Diffuse poorly differentiated lymphocytic lymphoma.—Eight of 25 patients (32%) with DPDL achieved a CR; the median duration of remission was 8.0 months (range, 3–72+), seven of eight patients having relapsed (table 2, fig 1). The only patient who has not relapsed is still in CR 72 months after completing CVP therapy. The median survival of CR patients has not yet been reached and 67% of them are still alive (the longest followup being 92 months). For those patients having a PR or no response (NR) the median survival is 10.4 months (range, 4–52+) (table 2, figs 3 and 4). This difference is highly significant ($P < 0.002$). The median survival for the entire group of DPDL patients was 23.2 months (fig 2).

Nodular poorly differentiated lymphocytic lymphoma.—Thirty-three of 49 patients (67%) with NPDL achieved a CR; the median duration of remission was 16 months (range, 3–79+), 21 patients (64%) having relapsed (table 2, fig 1). The median survival of CR patients was 94.9 months (range, 8+–102+), compared to 35.0 months (range, 1–87+) for NR and PR patients (figs 3 and 4). This difference is highly significant ($P < 0.001$). The median survival for the entire group of NPDL patients was 83.3 months (fig 2).

Nodular mixed histiocytic-lymphocytic lymphoma.—Twenty-four of 31 patients (77%) with NML achieved a CR. Since only four patients have relapsed, the median duration of remission has not yet been reached; 79% of patients are still in CR (the longest followup being 90 months). The median survival of CR patients has not yet been reached; 91% are still alive (the longest followup being 101

TABLE 2.—Non-Hodgkin's lymphoma: survival by response to therapy

Histology	Survival of complete responders: No. of patients	Survival of complete responders: Median survival (mos)	Survival of partial responders: No. of patients	Survival of partial responders: Median survival (mos)	Median survival of entire group (mos)
DWDL	7	84.0 (41–156+)	4	1, 5, 56+, 81+	78.2
DPDL	7	67% still alive; followup 28–92+ mos	18	10.4 (4–52+)	23.2
NPDL	33	94.9 (8+–102+)	16	35.0 (1–87+)	83.3
NML	24	91% still alive; followup 7–101+ mos	7	13.0 (4–32)	69% still alive
DML	1	51+	9	4.0 (1–32)	4.0
NHL	3	16, 20, 29	1	14	—
DHL	29	64% still alive; followup 3–116+ mos	33	7.0 (1–18)	11.0
DUL	3	3, 15+, 18+	4	5, 5, 6, 21	—

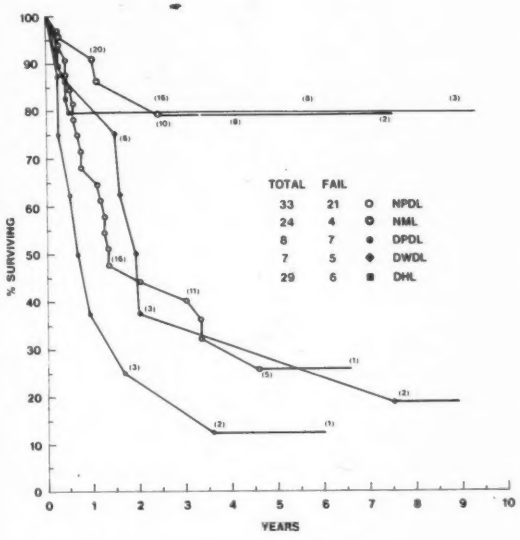

FIGURE 1.—Response duration (CR only).

months) compared to a median survival of 13.0 months (range, 4–32) for PR and NR patients (table 2, figs 3 and 4). This difference is highly significant ($P < 0.001$). The median survival for the entire group of NML patients has not been reached; 69% of all patients are still alive at 101+ months (fig 2).

Diffuse mixed histiocytic-lymphocytic lymphoma.—Only one of ten patients with DML achieved a CR, which continues at 44 months. The median survival of PR and NR patients was 4 months (range, 1–32), only one patient still being alive at 30+ months (fig 4). The median survival for the entire group of DML patients was 4 months (fig 2).

Nodular histiocytic lymphoma.—Of the four patients in this histologic group, three (75%) achieved a CR. All three, however, relapsed within 12 months (3, 4, and 12 months). All have died. Their survivals were 14, 16, 20, and 29 months (table 2).

Diffuse histiocytic lymphoma.—Twenty-nine of 62 DHL patients (47%) achieved a CR. Since only six patients achieving CR have relapsed, the median duration of remission has not yet been reached (fig 1); 74% of CR patients are still in remission (the longest followup being 111 months). The median survival of CR patients has also not been reached, with 64% of patients still alive (the longest followup being 116 months) compared to a median survival of 7 months (1–18 months) for PR and NR patients (table 2, figs 3 and 4). This difference is highly significant ($P < 0.001$). The median survival for the entire group of DHL patients was 11 months (fig 2).

Diffuse undifferentiated lymphoma.—Three of seven DUL patients (43%) achieved a CR. One relapsed at 3 months and two were still in remission at 10+ and 21+ months. The survival for CR patients was 3, 15+, and 18+ months compared to survivals of 5, 5, 6, and 21 months for PR and NR patients (table 2).

DURATION OF REMISSION AND SURVIVAL (Table 3)

The duration of remission of patients with non-Hodgkin's lymphomas also could be correlated with the histologic subgroup. Of DPDL patients only eight of 25 (32%) achieved a CR and seven of the

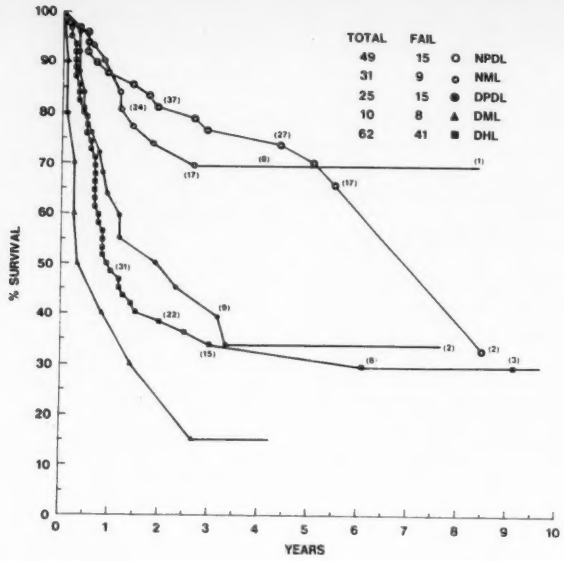

FIGURE 2.—Survival of all patients with non-Hodgkin's lymphoma.

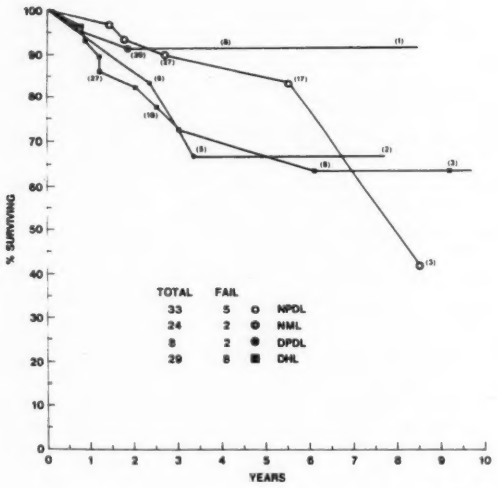

FIGURE 3.—Survival of complete responders.

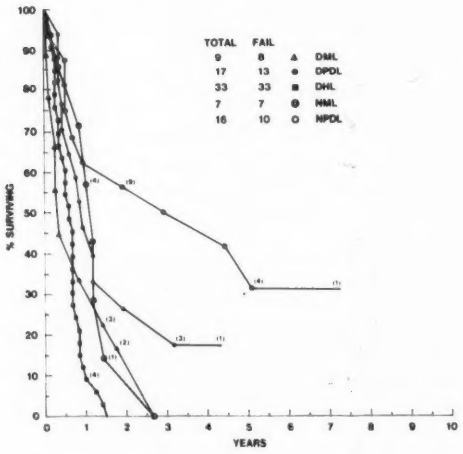

FIGURE 4.—Survival of patients with PR or NR.

TABLE 3.—Non-Hodgkin's lymphoma: response to combination chemotherapy

Histology	Total No. of patients	CR	
		No. of patients (%)	Median duration (mos)
DWDL	11	7 (64)	23.0 (4–107+)
NPDL	49	33 (67)	16.0 (3–79+)
DPDL	25	8 (32)	8.0 (3–72+)
NML	31	24 (77)	79% alive at 90+ mos
DML	10	1 (10)	44+
NHL	4	3 (75)	3,4,12, all relapsed
DHL	62	29 (47)	74% alive at 111+ mos
DUL	7	3 (43)	3,10+,21+

eight CR patients (88%) have relapsed. Of DHL patients, 29 of 62 (47%) achieved a CR; only six of the 29 CR patients (21%) have relapsed, all relapses occurring within 6 months of discontinuation of therapy. Of NPDL patients, 33 of 49 (67%) achieved a CR; 21 of the 33 CR patients (64%) have relapsed. In contrast to the early relapse pattern in DHL patients, NPDL relapses were seen as late as 55 and 63 months after discontinuation of therapy. In NML, 24 of 31 patients (77%) achieved a CR; four of the 24 CR patients (17%) have relapsed from 3 to 29 months after therapy. In DWDL, seven of 11 patients (64%) achieved a CR; five of the seven CR patients (71%) have relapsed.

Of those patients who achieved a CR, no significant differences were observed in projected survivals regardless of the cell type. However, numerous differences existed in the duration of remission. The duration of remission for DHL patients (74% free of disease at 111+ months) was significantly longer than the median duration of remission for DPDL patients of 8 months ($P < 0.01$). The duration of remission for NML patients (79% free of disease at 90+ months) was significantly longer than the median durations of remission of 16 months for NPDL patients ($P < 0.003$), 8 months for DPDL patients ($P < 0.002$), and 23 months for DWDL patients ($P < 0.03$).

When all patients in each histologic category are compared, significant differences in survival are apparent. The median survival for NPDL patients of 83.3 months was longer than that for DPDL patients of 23.2 months ($P < 0.001$). Similarly, the survival for NML patients (69% alive at 101+ months) greatly exceeded the median survival for DML patients of 4 months ($P < 0.001$). In addition to nodal architecture, cellular differentiation also has prognostic significance. The median survival for DWDL patients of 88.2 months exceeds that for DPDL patients of 23.2 months ($P < 0.04$), which in turn exceeds that for DML patients of 4 months ($P < 0.03$). The median survival for DHL patients of 11 months is slightly better than the median survival for DML patients of 4 months; this difference in survival is not statistically significant ($P = 0.09$). The median survival for DHL patients is not significantly less than the median survival for DPDL patients of 23.2 months ($P \geq 0.13$).

As has been previously reported (4), there was a close correlation between sites of relapse and sites of initial involvement in non-Hodgkin's lymphoma patients achieving a CR. Eighty-one percent of patients relapsed in lymph nodes; other sites of relapse (usually but not always accompanied by lymph node relapse) included bone marrow (10%), liver (6%), central nervous system (6%), and peripheral blood (4%). It is apparent that extranodal sites of disease *proved by restaging techniques to be free of disease* are rarely the site of relapse in those who achieve a CR.

Toxicity (Table 4)

All three regimens produced transient but significant leukopenia in virtually all patients at some point in the course of their induction therapy. There were 19 episodes of documented bacterial infection secondary to chemotherapy-induced leukopenia; seven of these were fatal. Two patients with extensive stage IV disease and compromised organ function experienced fatal sepsis in the first month of therapy. Five patients developed fatal sepsis during the latter cycles of induction therapy; the disease was responding in three patients and was progressing in two.

Eight patients had herpes zoster (two localized, three widespread, and three disseminated); these cases tended to occur after multiple cycles of chemotherapy. This infection developed in three patients who had achieved a CR. One patient with NHL died of presumed focal myocarditis associated with

TABLE 4.—Toxicity of combination chemotherapy regimens*

Toxicity	No. of patients receiving— CVP (103 patients)	C-MOPP (51 patients)	BACOP (37 patients)
Bacterial infections	8 (4)	5 (1)	6 (2)
Fungal infections	1	0	1
Herpes zoster	0	3 (1)	5
Thrombocytopenic hemorrhage	3	1	1
Hemorrhagic cystitis	7	1	0
Pulmonary fibrosis	0	0	4

*Nos. in parentheses are patients with fatal complications.

disseminated herpes zoster at the end of the sixth cycle of C-MOPP re-induction, having relapsed after a 12-month remission. At autopsy no gross evidence of residual tumor was found.

Clinically evident hemorrhagic cystitis developed in eight patients, predominantly those receiving CVP therapy. Pulmonary fibrosis developed in four of the first 16 patients receiving BACOP therapy. Following reduction of the dose of bleomycin from 15 to 5 units/m^2, no additional cases of pulmonary fibrosis have been observed in 18 subsequent patients.

Four patients developed a second malignancy. A NPDL patient with a significant history of smoking died of large-cell anaplastic carcinoma of the lung 71 months after initiation of CVP therapy. Another NPDL patient developed a leiomyosarcoma at the site of a previously resected leiomyoma 12 months after completion of CVP therapy; this patient is still alive and both diseases are in CR. A DHL patient in a CR developed duodenal carcinoma 18 months after completion of C-MOPP therapy; she died of duodenal carcinoma 12 months later and at autopsy no evidence of lymphoma was found. Another DHL patient received 8 years of single alkylating agent therapy for NPDL before a change in histology to DHL at the time of relapse. She achieved a CR after 6 months of BACOP therapy, but developed acute myelogenous leukemia 1 month later and subsequently died of her leukemia.

DISCUSSION

Our experience using the combinations of CVP, C-MOPP, and BACOP in advanced disease demonstrates that 54% of all non-Hodgkin's lymphoma patients can achieve a CR. Nodularity and well-differentiated lymphocytic histology favor both response and survival, once again confirming that the Rappaport classification has clinical prognostic relevance. Furthermore, this histologic classification identifies subgroups of patients who can be expected to have a sustained remission and those who will not.

Detailed staging of non-Hodgkin's lymphoma patients has led to the realization that most patients have widely disseminated disease at the time of diagnosis (6–8). In a detailed, systematic staging study previously reported and presented at this symposium, Chabner et al (5) demonstrated that 86% of all non-Hodgkin's lymphoma patients have stage III or IV disease at the time of diagnosis. This information has provided the basis for a more rational design of clinical trials.

Nodular lymphoma patients have a 71% CR rate compared to a 41% CR rate for diffuse lymphoma patients; nodular lymphoma patients have a longer median survival (78.9 months) than diffuse lymphoma patients (14.9 months) ($P < 0.001$). This difference in survival correlates with the higher CR rate in nodular lymphoma patients because (*a*) no significant differences in survival existed between patients who achieved a documented CR, regardless of the histologic type; and (*b*) no significant differences in survival existed between patients who failed to achieve a documented CR, regardless of histologic type (with the possible exception of DWDL patients of whom too few have been treated to accurately define survival). What is significant is that patients with certain histologic subtypes (NML, DHL) have a prolonged disease-free survival, while other patients (NPDL, DPDL) have a duration of survival which does not correlate with the length of their initial remission.

DWDL has a very favorable prognosis. These patients tend to have a high CR rate (67%) and a moderately long duration of remission (23 months). At the time of relapse the disease, in most patients, is still sensitive to combination chemotherapy, thus the median duration of survival is very long (84 months). Two of the four partial responders also had prolonged (48+ months) responses. NPDL patients also do well. Sixty-seven percent of NPDL patients achieved a CR, but its duration was relatively short (16 months); however, patients who previously achieved a CR were usually responsive to re-

institution of the same chemotherapy. Of 33 patients who achieved a CR, 22 (67%) have relapsed; however, nine of these 22 (41%) have achieved a second CR with CVP. While all NPDL patients have a relatively good prognosis, this histologic group biologically behaves as though it were two distinct patient populations. Thus, although the median survival for all NPDL patients was long (83.3 months), there is a significant difference in median survival between patients who initially achieved a CR (94.9 months) and those who did not (35 months) ($P < 0.001$). In contrast, DPDL patients have a poor prognosis. The initial CR rate was low (32%), the duration of remission was short (8 months), and the median survival for all DPDL patients was only 23.2 months. Although seven of eight CR patients have relapsed, the survival of CR patients (67% alive at 92+ months) is significantly longer than that of PR and NR patients (10.4 months; $P < 0.002$). New treatment regimens are clearly needed for patients with DPDL to increase the initial CR rate and the duration of remission.

In patients with mixed histiocytic-lymphocytic lymphoma the presence or absence of nodularity has profound implications. NML patients have a very high CR rate (77%), a very long remission duration (79% still in CR at 90+ months), and a very long survival (91% still alive). Those patients who fail to achieve a CR have a significantly shorter median survival (13 months; $P < 0.001$). Thus, the excellent prognosis for all NML patients (69% still alive at 101+ months) is due to the ability to achieve a high CR rate and a long unmaintained remission. In contrast, only one of ten patients with DML achieved a CR. The median survival for NML patients was, therefore, much greater than that for DML patients (4 months; $P < 0.001$).

The other group of patients with a malignant "histiocytic" or large-cell component, DHL, also has a prognosis closely related to the ability to achieve a CR. Only six of 29 CR patients have relapsed (21%) and no patient has relapsed later than 6 months after completion of therapy. The short median survival for all DHL patients (11 months) occurs because less than half of the patients achieve a CR. However, for those who do achieve CR the survival is very long. The median has not been reached (64% alive at 111+ months). For patients with DHL, the response rates were not significantly different between the C-MOPP (or MOPP) regimen and the BACOP regimen. Recent detailed analysis of clinical presentations indicates that stage IV disease, or specific patterns of involvement (ie, bone marrow, gastrointestinal tract, or a large tumor burden) are poor prognostic factors which must also be considered when evaluating therapeutic efficacy (19).

This study re-emphasizes the importance of achieving an initial CR in prolonging survival, not only in the diffuse but also in the nodular lymphomas. For the first time it can be clearly demonstrated that a CR significantly increases survival even in patients with "favorable" histologies such as nodular lymphocytic and NML. It is of interest that the prolonged survival for NML is due to a prolonged initial remission duration whereas NPDL patients, with a comparable prognosis, tend to relapse but respond again to repeat combination chemotherapy. Unlike NML patients, these patients do not remain disease-free when not receiving chemotherapy. These data indicate that in therapeutic trials these two histologic subtypes should be analyzed separately because a difference in ultimate survival may develop if current remission duration and survival patterns persist. Because nodular lymphoma patients have a more favorable prognosis than diffuse lymphoma patients it has been suggested that these patients be treated less aggressively. Attempts to compare response rates of various treatment modalities from different institutions have been compromised by the lack of uniformity in histologic classification and the frequent absence of information concerning long-term duration of remission and survival. The only prospective randomized study comparing single-agent chemotherapy to combination chemotherapy with and without radiotherapy has thus far not shown any difference in response rate or survival, although the CVP-radiotherapy arm of the study appeared to be too toxic (20). Caution must be exercised to avoid any premature judgment concerning the relative efficacy of the regimens utilized. First, the followup period is relatively brief (approximately 2 years), and based upon data from this study, differences in survival would not be expected for an additional 2–3 years of followup. Second, the responses of NML patients have not been analyzed separately from those of NPDL patients and important differences between these two groups are now apparent. Third, the difference between achieving a CR versus a PR in our study is now known to be important, so that interpretation of any data must be based on careful evaluation of restaging criteria.

In summary, combination chemotherapy can be effectively administered to patients with advanced non-Hodgkin's lymphomas. Patients with nodular lymphomas have a favorable prognosis although new modalities of therapy to prolong the remission duration of NPDL patients could further improve their survival. New therapeutic approaches must be developed for DHL patients with poor prognostic

factors and for patients with DPDL, DML, and DUL. New approaches might include the development of new chemotherapy regimens or the addition of radiotherapy and/or immunotherapy to existing treatment regimens. The evaluation of beneficial and adverse effects calls for the diligent application of prognostically proved histologic classification, careful staging and restaging, and prolonged observation, particularly in patients with nodular lymphoma.

LIST OF COMPOUNDS

Adriamycin: NSC-123127; CAS reg. No. 23214-92-8
BACOP = bleomycin, adriamycin, cyclophosphamide, vincristine, and prednisone
Bleomycin: NSC-125066; CAS reg. No. 11056-06-7; [2,4′-bithiazole]-4-carboxylic acid, 2′-(2-aminoethyl)-, monohydrate
C-MOPP = cyclophosphamide, vincristine, prednisone, and procarbazine
CVP = cyclophosphamide, vincristine, and prednisone
Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate
Mechlorethamine: NSC-762; CAS reg. No. 55-86-7; diethylamine, 2,2′-dichloro-*N*-methyl-, hydrochloride
Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-
MOPP = mechlorethamine, vincristine, prednisone, and procarbazine
Prednisone: NSC-10023; CAS reg. No. 53-03-2; pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-
Procarbazine: NSC-77213; CAS reg. No. 491-88-3; *p*-toluamide, *N*-isopropyl-α-(2-methylhydrazino)-, monohydrochloride
Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1)

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Chemotherapy of Non-Hodgkin's Lymphoma: 10 Years' Experience in the Southwest Oncology Group [1]

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SUMMARY

The Southwest Oncology Group (SWOG) has completed five studies of high-dose intermittent combination chemotherapy for the management of advanced (stage III and IV) non-Hodgkin's lymphoma involving 1143 patients from May 1966 to September 1974. Lack of uniform histopathologic interpretation precludes precise analysis of these data. Although there has been little change in complete response duration over the years of this study, there has been an overall improvement in response rate and survival though there is no statistically significant improvement in the best overall survival when compared to the Stanford experience in stage III and IV disease (1960–71). The response rate and survival in diffuse histiocytic lymphoma have improved since the first study. There is definite evidence of a plateau in the survival curve beyond 2 years. The percentage of survival at which the plateau appears has increased over the years to 40% in the most recent studies, and the survival is suggestively better than the Stanford experience ($P = 0.09$). Over the years there has been a distinct improvement in response rate and survival of patients with nodular lymphocytic lymphoma, although the best SWOG survival is no different than the Stanford experience ($P = 0.36$).

[Cancer Treat Rep 61:1067–1078, 1977]

Since the initial reports on the use of high-dose intermittent combination chemotherapy in the management of non-Hodgkin's lymphoma (NHL) (1,2), there has been a great proliferation of reports dealing with the management of these diseases. Between May 1966 and September 1974, the Southwest Oncology Group (SWOG) completed five major cooperative studies involving 1143 patients (table 1). Although the SWOG studies, as well as others, have employed new and inventive therapeutic approaches, any analysis that attempts to compare one therapeutic program with another faces certain basic difficulties; these include differences in histopathologic interpretation and other prognostic factors as well as definition of complete response.

Until recently, the management of NHL has been based on imprecise histopathologic criteria. Although Rappaport et al (3) first formulated a working classification of NHL in 1956, only recently has it replaced the inadequate terminology of lymphosarcoma, reticulum cell sarcoma, and giant follicular lymphoma. This classification was first validated by a detailed retrospective review of 405 cases at Stanford (4) in which a single experienced hematopathologist reclassified each diagnostic tissue sample. The clinical usefulness of the Rappaport classification has now been substantiated by many prospective studies.

In the initial SWOG report on the treatment of NHL, the older terminology was used and there

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TABLE 1.—SWOG dosage schedules in NHL studies

Regimen	Drug	Dose	Duration	Schedule	Interval (wks)
COP 1 (SWOG-753)	Cyclophosphamide	800 mg/m²/day	Day 1	Single iv infusion	2
	Vincristine	2 mg/m²/day	Day 1	Single iv infusion	2
	Prednisone	60 mg/m²/day	8 days	Taper after Day 5	2
COP 2 (SWOG-760)	Cyclophosphamide	100 mg/m²/day	14 days	Single oral dose	4
	Vincristine	1.4 mg/m²/day	Days 1 and 8	Single iv infusion	4
	Prednisone	60 mg/m²/day	8 days	Taper after Day 5	4
COP 3 (SWOG-765)					
Treatment 1	*See* COP 1				
Treatment 2	Cyclophosphamide	400 mg/m²/day	Day 1	Single iv infusion	2
	Vincristine	1.4 mg/m²/day	Day 1	Single iv infusion	2
	Prednisone	100 mg/day	5 days	50 mg bid	2
	ARA-C	50 mg/m²/day	Days 2–5	Single iv infusion	2
Treatment 3	Mechlorethamine	6 mg/m²/day	Days 1 and 8	Single iv infusion	4
	Vincristine	1.4 mg/m²/day	Days 1 and 8	Single iv infusion	4
	Prednisone	40 mg/m²/day	10 days	Divided oral doses	4
	Procarbazine	100 mg/m²/day	10 days	50 mg, Day 1; 100 mg, Day 2	4
COP 4 (SWOG-780)	Cyclophosphamide	125 mg/m²/day	14 days	Single oral dose	4
	Vincristine	1.4 mg/m²/day	Days 1 and 8	Single iv infusion	4
	Prednisone	60 mg/m²/day	5 days	Divided oral doses	4
	Bleomycin	10 units/m²/day	Days 2–5	Single iv infusion	4
CHOP/HOP (SWOG-7204)					
Treatment 1	Cyclophosphamide	750 mg/m²/day	Day 1	Single iv infusion	2
	Adriamycin	50 mg/m²/day	Day 1	Single iv infusion	2
	Vincristine	14 mg/m²/day	Day 1	Single iv infusion	2
	Prednisone	100 mg/day	5 days	25 mg orally qid	2
Treatment 2	Adriamycin	80 mg/m²/day	Day 1	Single iv infusion	2
	Vincristine	1.4 mg/m²/day	Day 1	Single iv infusion	2
	Prednisone	100 mg/m²/day	5 days	25 mg orally qid	2

was no central pathologic review (5). In 1967, the Lymphoma Pathology Review Panel and Central Repository under the direction of Dr. Henry Rappaport was established to aid the cooperative groups by providing more uniform and consistent interpretation of pathologic material from patients entered in various group studies (5).

Over the years an increasing number of SWOG cases have been submitted to the Lymphoma Review Panel, but submission of slides was not mandatory for study eligibility until the initiation of the currently active group study (SWOG-7426). (The results of this ongoing trial are not included in this report.) This lack of homogenous interpretation of diagnostic histopathologic material makes precise comparisons of the various SWOG studies and comparisons with other group and independent studies more difficult. However, a recently completed analysis of pathologic diagnoses rendered by contributing institutional pathologists compared to those determined on review by Drs. James Butler or Gerald Byrne, Jr (for the Lymphoma Review Panel), provided means whereby the SWOG studies could be compared with reasonable accuracy to the results from other studies in which pathologic interpretation has been more consistent over the years. For instance, 96% of the patients entered in the SWOG studies could be confirmed to have NHL on review.[6] Furthermore, two distinct subtypes of NHL were most often correctly diagnosed at the institutional level: 86% of the cases of diffuse histiocytic lymphoma (DHL) and 78% of the cases of nodular lymphocytic lymphoma (poorly differentiated [NLPD] and well differentiated) were confirmed on review. Significantly less agreement was noted for all other subtypes of NHL. A similar analysis (unpublished) was done in 1972 on the earlier cases submitted for review, and the findings were essentially identical,[7] indicating that there has been little variation in interpretation of NHL by the contributing institutions' pathologists throughout the 10 years of these five studies.

[6]Jones SE, Butler JJ, Byrne GE, et al. Histopathologic review of lymphoma in the Southwest Oncology Group. Cancer 39:1071–1076, 1977.

[7]Coltman CA, Jr. Unpublished data.

TABLE 2.—Histologic classification of partially and fully evaluable patients in 2 SWOG NHL studies compared with those in the Stanford study

Histology	COP (%)				CHOP/HOP (%)		Stanford (%)
	1	2	3	4	Review panel	Review panel + institution	
Diffuse histiocytic	53 (54)	49 (35)	101 (43)	16 (23)	46 (32)	137 (31)	65 (26)
Nodular histiocytic	0 (0)	0 (0)	4 (02)	3 (04)	11 (08)	20 (05)	17 (07)
Diffuse lymphocytic, poorly differentiated	36 (37)	64 (46)	57 (24)	22 (31)	17 (12)	77 (18)	27 (11)
Nodular lymphocytic, poorly differentiated	3 (03)	17 (12)	34 (14)	15 (21)	49 (34)	116 (27)	52 (21)
Diffuse lymphocytic, well differentiated	5 (05)	8 (06)	20 (09)	10 (14)	9 (06)	41 (09)	6 (02)
Diffuse nodular	0 (0)	1 (01)	7 (03)	2 (03)	5 (03)	24 (05)	28 (11)
Nodular mixed	1 (01)	0 (0)	12 (05)	3 (04)	7 (05)	22 (05)	51 (21)
Unclassified	51	15	66	3	0	28	9

Table 2 shows the histologic classification of all partially and fully evaluable patients, who did not have extensive prior therapy, in each SWOG study as well as those patients with stage III and IV NHL treated with both chemotherapy and radiotherapy reported by Jones et al (4) from Stanford.[8] The tabulation is based on the contributing institutional pathologists' interpretation of the Lymphoma Review Panel's interpretation in those instances where it was available. Thirty-three percent of the diagnostic tissue from the cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP)/adriamycin, vincristine, and prednisone (HOP) study was reviewed (Review Panel) and compared to the entire group in which the Lymphoma Review Panel's diagnosis was used when available (Review Panel plus institution) (table 2). There are no significant differences in percentage of the various subgroups in this histologic comparison of CHOP/HOP. An analysis of response rates and survival in these two groups shows no significant difference to date.[9] Further examination of table 2 shows apparent variation in the composition of the subgroups in each SWOG study over the years, but pathology review was not employed for the majority of cases.

The Stanford data (table 2), which were subject to review by a single hematopathologist, include a significantly larger composition of mixed histologies (both nodular and diffuse) than those of any of the SWOG studies, including the one third of CHOP/HOP entries submitted to the Lymphoma Review Panel. This preponderance of mixed cell types of NHL has not been evident in two recent studies from Stanford (6,7). These variations in histologic composition serve to emphasize the importance of comparing single and homogenous histologic groups from one study to another within the SWOG or when comparing SWOG studies to other groups or independent trials.

This review will begin with an overview of each of the SWOG studies and will make some general comments on response and survival.

There has been a uniform definition of complete response in all of the SWOG studies, as well as a uniform interpretation of complete response, by virtue of having a single principal study coordinator in four of the five studies (Dr. J. K. Luce). The response rate, remission duration, and survival will then be examined in those two histologic subgroups (DHL and NLPD) in which there is approximately an 80% chance that the institutional pathologists' interpretation would be confirmed by the Lymphoma Review Panel.[10] All patients diagnosed as DHL and NLPD in the five SWOG studies are analyzed separately with respect to response, remission duration, and survival.

This analysis shows that there has been an *overall* improvement in response rate and survival since the first SWOG study, but little change in complete response duration. There is, however, no statistically significant improvement ($P = 0.59$) when the best overall SWOG survival (cyclophos-

[8]The authors acknowledge the generous cooperation of Saul A. Rosenberg, MD, for providing the raw data on the 405 patients originally reported (4) from Stanford, from which the data on the 254 stage III and IV patients were derived.

[9]McKelvey EM (coordinator of SWOG-7204). Personal communication.

[10]See footnote 6.

phamide, vincristine, and prednisone, COP 4) is compared to the Stanford experience reported by Jones et al (4).

The response rate and survival for DHL have also improved since the first study. There is definite evidence of a plateau which appears in the survival curve beyond 2 years.

Of the 356 patients with DHL who were entered into the five studies, 218 (61%) have died but only 21 (10%) have died after 2 years. Forty-nine percent (67 of 138 patients) of the remaining patients are alive after 2+–7+ years.

There has been distinct improvement over the years in response rate and survival of NLPD, although the survival of the best arm of the SWOG studies (CHOP, 1972–76) is no different than the Stanford experience (1960–71; $P = 0.36$).

REVIEW OF THE SWOG

Overall Results

The SWOG initiated studies with high-dose intermittent combination chemotherapy in May 1966, using COP in patients with advanced NHL (5) (table 1). One hundred and forty-nine[11] fully and partially evaluable patients that did not have extensive prior therapy (this category includes patients with early death as well as inadequate trials because of toxicity, patients refusing further therapy, and patients lost to followup) received 800 mg/m² of cyclophosphamide on Day 1, 2 mg/m² of vincristine on Day 1, and 50 mg/m² of prednisone on Days 1–5 which is quickly tapered by Day 8. This regimen was designed to combine in full dose three drugs with differing dose-limiting toxicities. Patients were treated for a minimum of six treatments.

Four consolidation treatments were given after complete response at the same dose level. Patients in complete response after a minimum of ten cycles were randomly allocated to either no further treatment or continued treatment with COP at 4-week intervals. The 149 fully and partially evaluable patients achieved an overall complete response rate of 35% and a partial response rate of 36% (table 3). The median duration of maintained response was longer than that of unmaintained response. These response curves appeared to fit a straight line on a semilog plot, indicating that the response duration was approximately exponentially distributed, and that the relapse rate with time was constant. The overall median duration of survival was 80.9 weeks (with a similar configuration of the survival curve). The complete response rate was clearly better than that described for most single agents, but the median duration of complete response was not significantly improved, suggesting that this combination did not improve the quality of response.

Although intensive pulse treatment provided the best therapeutic index for rapidly proliferating tumors, eg, choriocarcinoma (8) and Burkitt's lymphoma (9), a more protracted treatment might be of benefit in the management of slower growing tumors such as NHL. Furthermore, at the beginning of the second SWOG NHL study, the most effective program reported in disseminated Hodgkin's disease was the mechlorethamine, vincristine, prednisone, and procarbazine (MOPP) program, later reported by DeVita and associates (10). The second SWOG study was COP 2 (table 1), in which the cyclophosphamide was administered orally at a dose of 100 mg/m²/day × 14 days, the vincristine was given at a dose of 1.4 mg/m² on Days 1 and 8, and no change was made in the prednisone schedule.

This regimen was repeated every 28 days, and after a minimum of six cycles, patients in complete response were given four consolidation treatments. A random half of the patients were continued on maintenance therapy every 4 weeks for four cycles and then every 8 weeks; the other half received no further treatment. Between May 1968 and August 1969, 154 patients received this regimen and achieved a complete response rate of 49% and a partial response rate of 35% (table 3). The overall duration of complete response was 109.3 weeks, and those on maintenance therapy had a more prolonged response duration than those off therapy. The overall survival, 150.6 weeks, was significantly better than that achieved by COP 1 ($P = 0.003$).

The combination of an alkylating agent and cytosine arabinoside (ARA-C) had been proved to be highly synergistic in a number of experimental systems (11,12). The most effective schedule was that of an alkylating agent in a large single dose followed by either continuous or daily treatment with ARA-C. Phase I studies indicated that cyclophosphamide at a dose of 400 mg/m² followed by ARA-C at a level of 100 mg/m²/day × 4 days was well tolerated. With this in mind, ARA-C was added to the COP 1 regimen at a dose of 50 mg/m² on Days 2–5 with an attenuated dose of cyclophosphamide of 400 mg/m² on Day 1.

MOPP had been shown to be highly effective in the management of Hodgkin's disease by both the NCI (10) and the SWOG (13). In preliminary SWOG studies, MOPP had been shown to be effective in patients with NHL. The objective of COP 3 (table 1) was to determine the relative effectiveness of the

[11]The number differs from the 140 in the original publication (5) because it now includes partially and fully evaluable patients.

TABLE 3.—SWOG studies in NHL

Study	Patients	Complete response (%)	Median duration of complete response* (wks)	Median survival duration* (wks)
Overall results				
COP 1	149	52 (35)	—	80.9
COP 2	154	76 (49)	109.3	150.6
COP 3	301	137 (46)	220.5	117.6
COP 4	74	51 (69)	109.7	176.2
CHOP/HOP	465	268 (58)	123.3	NR
Stanford	255	—	—	165.0
Results in DHL				
COP 1	53	12 (23)	—	29.7
COP 2	49	24 (49)	60.7	71.1
COP 3 ± ARA-C	65	22 (34)	197.4	66.7
COP 3-MOPP	36	34 (29)	114.3	39.7
COP 4	16	10 (63)	107.0	44.7
CHOP	68	32 (47)	101.1	47.9
HOP	69	38 (55)	95.5	87.5
Stanford	65	—	—	47.3
Results in NLPD				
COP 1	3	0	—	—
COP 2	17	9 (53)	NR	154.4
COP 3 ± ARA-C	20	14 (70)	NR	198.7
COP 3-MOPP	14	6 (43)	NR	132.2
COP 4	15	10 (67)	152.0	184.3
CHOP	62	48 (77)	NR	NR
HOP	54	32 (59)	NR	NR
Stanford	52	—	—	388.1

*NR = not reached.

original COP 1 regimen compared to COP + ARA-C and MOPP. Patients in the COP ± ARA-C regimens were treated at 2-week intervals for a minimum of ten cycles and then maintained on the same regimens at 4-week intervals.

Patients treated on the MOPP regimen received a minimum of six cycles at 4-week intervals; patients with a documented complete response continued to receive treatment at 56-day intervals.

Between August 1969 and November 1971, 301 patients with NHL were entered into the three treatment arms of this study. The overall complete response rate was 46% (COP, 47%; COP + ARA-C, 48%; MOPP, 40%) and the partial response rate was 27% (table 3). The median duration of complete response was 220.5 weeks, which reached statistical significance compared to the response duration of COP 2 ($P = 0.04$). The overall survival, 117.6 weeks, suggests superiority to COP 1 ($P = 0.07$).

A variety of investigators have demonstrated that bleomycin has activity as a single agent in advanced NHL (14). Because of its relative lack of myelosuppressive activity, it was considered ideal for addition to combinations of prototype antitumor agents. Dose-limiting toxicity usually consisted of pulmonary insufficiency and fibrosis, particularly in older patients and in those receiving larger doses of the drug. With this in mind, bleomycin was added to the COP 2 regimen (in which the cyclophosphamide dose was increased to 125 mg/m²) at a dose of 10 units/m² iv on Days 2–5 of each cycle to a total dose of 300 units (table 1). This cycle was repeated every 28 days. Those who achieved complete response following a minimum of eight cycles were re-evaluated and put on maintenance treatment with COP 2 at increasing intervals.

A total of 74 patients were entered in this study between November 1971 and April 1972 (table 3). The overall complete response rate was 69% and the partial response rate was 27%, the highest response rate yet reported by SWOG.

Leukopenia and probably bleomycin-induced pulmonary toxicity were significant factors in this study. Seventy-four percent of the patients experienced severe leukopenia and two patients died from pneumonia complicating leukopenia. Five older patients either died or sustained life-threatening pulmonary complications attributed to bleomycin. Because of this unacceptable toxicity in older patients, the study was closed and has only recently been reopened. The bleomycin dose has been adjusted to 4 units/m² on Days 1 and 8 of each cycle of COP as

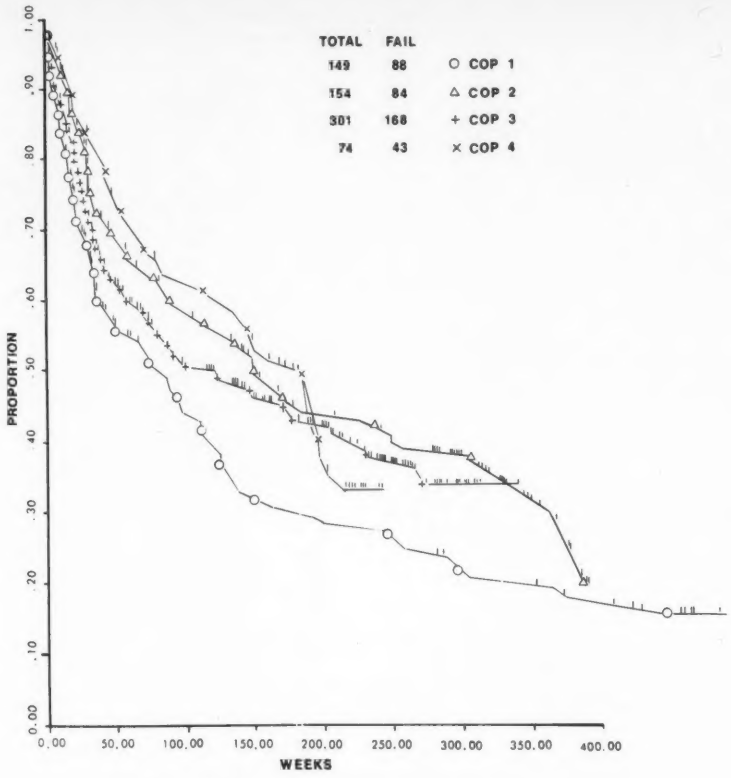

FIGURE 1.—Survival of all patients receiving COP 1–4.

one of the treatment arms in the ongoing study (not reported here).

The median duration of complete response of 109.7 weeks for COP 4 was significantly lower than COP 3 ($P = 0.05$). The median duration of survival represented the best yet, 176.2 weeks. It was better than COP 1 ($P = 0.004$) but not superior to COP 2 ($P = 0.64$) or COP 3 ($P = 0.12$). Figure 1 compares the survival curves for COP 1 through the four studies plotted by the Kaplan and Meier method (15). The significance of the differences in the survival curves was calculated by a generalized Wilcoxon test (16).

The new anthracycline antibiotic, adriamycin, had been used both alone and in combination in patients with lymphoma of various types (17). The most recently completed SWOG study in NHL was based upon a pilot study (18) in which adriamycin was added to COP (CHOP) with a high complete response rate (seven of nine patients) and good tolerance. The fifth SWOG study compared CHOP with HOP (table 1). Patients were randomly assigned to receive CHOP or HOP. After achieving a complete response, they received three additional consolidation treatments at the same dosage. Those who remained in complete response were randomly assigned to maintenance therapy with COP or OAP, in which ARA-C was substituted for cyclophosphamide. Maintenance therapy was continued at 21- to 28-day intervals until relapse or until 18 months of treatment was completed.

Between April 1972 and September 1974, 465 partially and fully evaluable patients were randomly assigned to CHOP or HOP. The overall complete response rate was 58% (table 3) and the partial response rate 21%. The complete response favored CHOP over HOP although the difference was not statistically significant. The median duration of maintained remission was 114.0 weeks, with CHOP always better than HOP ($P = 0.17$). The median survival has yet to be reached. Of 115 patients maintained on COP, 75% remained in complete response after 1 year. For the 108 patients maintained on OAP, 60% remained in complete

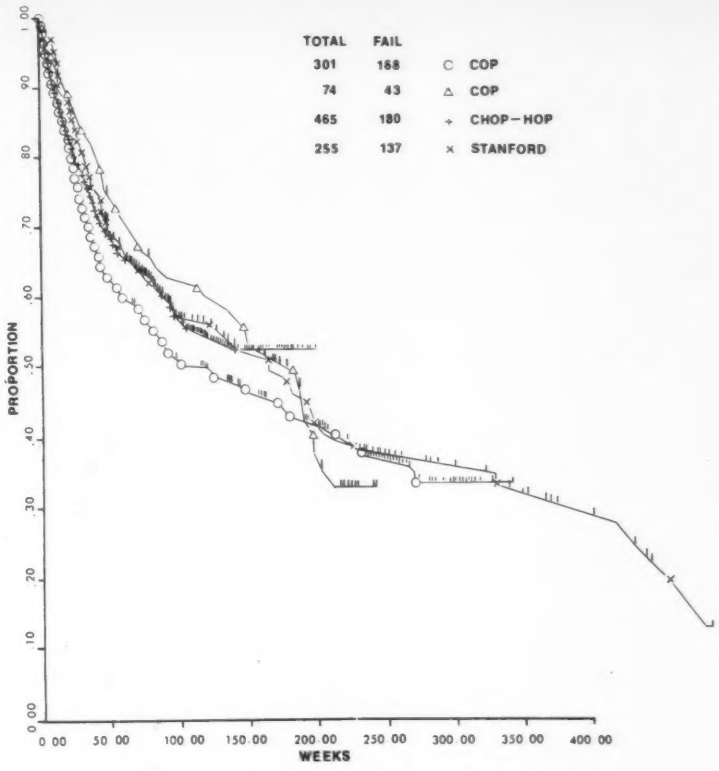

FIGURE 2.—Survival of all patients in the COP 3 and 4, CHOP/HOP, and Stanford studies.

response at 1 year. The highest number of relapses have occurred in patients who never received cyclophosphamide (HOP induction + OAP maintenance).

Leukopenia, thrombocytopenia, and infection were severe in both arms of the study. Although there were no significant differences in the types or degrees of toxicity in the two study arms, 11 patients died during the CHOP regimen and seven during the HOP regimen. Drug-related congestive heart failure occurred in two patients on each arm, but it was reversible with discontinuance of the adriamycin.

Figure 2 shows the overall survival curves of all patients with NHL who were treated with COP 3, COP 4, or CHOP/HOP, and also shows the Stanford survival experience (1960–71). There are no significant differences between these curves for total survival (all P values ≥ 0.12).

Results With Histiocytic Lymphoma

Each SWOG study arm was examined with respect to the response rate, response duration, and survival of patients with DHL (table 3). COP 1 and COP + ARA-C or COP 3 were combined because of their comparability (COP ± ARA-C).

The complete response rate varied from a low of 23% in the COP 1 study to a maximum of 63% in the COP 4 study. Similarly, the median duration of complete response varied from 61 weeks in COP 2 to 197.4 weeks in the COP ± ARA-C arms of COP 3. The median survivals show similar variability. There is, however, no statistically significant difference between these values.

Figures 3 and 4 show the survival curves for the five SWOG regimens compared to the survival of patients with stage III and IV DHL from Stanford

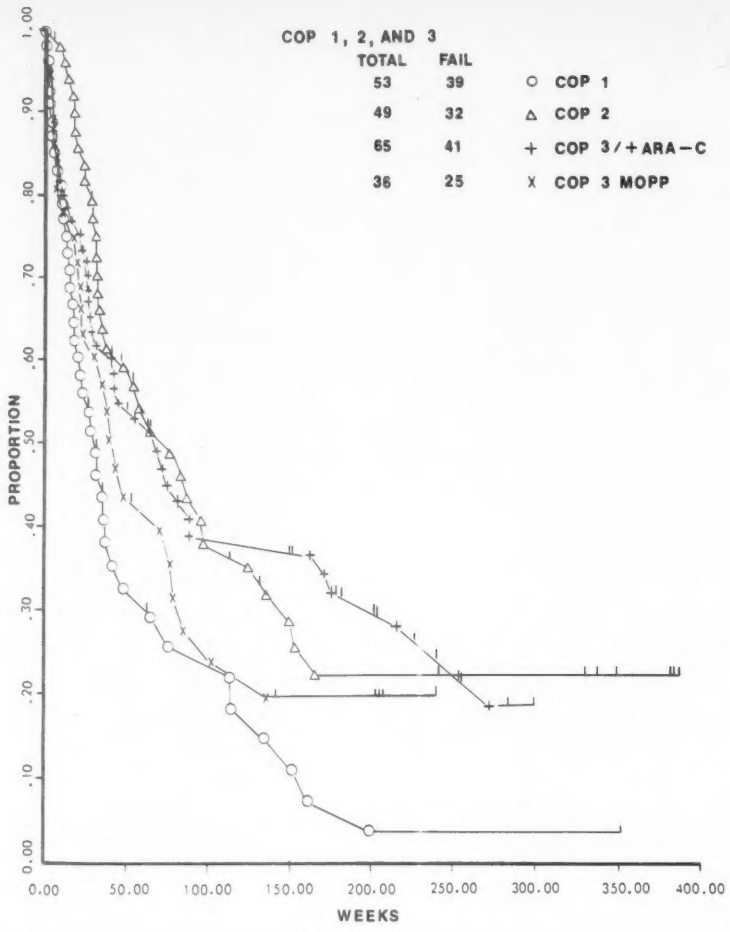

FIGURE 3.—Survival of DHL patients in the COP 1 and 2, COP 3 ± ARA-C, and COP 3–MOPP studies.

(1960–71). The Stanford patients for the most part received only single-agent chemotherapy (19), but were treated during approximately the same period of time. In each SWOG study there is definite evidence of a plateau in the survival curve beyond 2 years. Of the 356 DHL patients entered in these five SWOG studies, 197 have died within the first 2 years, but only 21 patients (10% of the deaths) have died after 2 years. Forty-nine percent of the living patients (67 of 138 patients) remain alive from 2+ to 7+ years. We may be defining an increasing population of DHL patients who have been cured by chemotherapy (20). The data for HOP are suggestively superior to those of the Stanford single-agent treatment ($P = 0.09$). Patients on the HOP induction regimen had the fewest relapses when maintained on OAP.[12]

Results With NLPD

In table 3 all NLPD patients are listed with respect to response rate, response duration, and

[12] *See* footnote 9.

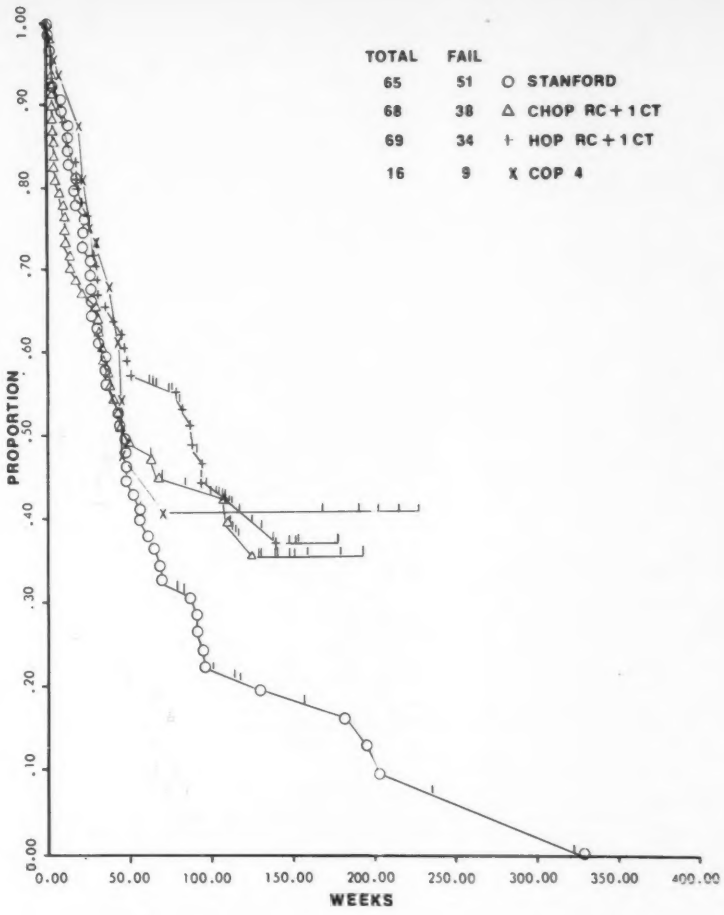

FIGURE 4.—Survival of DHL patients in the COP 4, CHOP, HOP, and Stanford studies.

survival. The response rates varied from 43% with MOPP to 77% with CHOP. In five of six instances the median duration of complete response had not been reached and in two of seven instances the median survival had not been reached.

Figures 5 and 6 show the survival curves of NLPD patients in the five studies with the retrospective Stanford data for comparison. CHOP and HOP are comparable to the Stanford data (P = 0.36 and 0.77 respectively). There is a suggestion that the Stanford data are superior to COP 4 (P = 0.12).

The SWOG studies in NHL have methodically attempted to define response rate, response duration, and survival in a heterogenous population of lymphoma patients with a general trend toward improvement in the past 10 years. The absence of a uniform hematopathologic classification and the lack of centralized hematopathologic review have compromised the definitive review of these data. The failure to establish rigid criteria for the definition of completeness of response has been an additional problem obscured by the many maintenance programs (21). These problems have been remedied in the currently active SWOG NHL study (SWOG-7426) in which hematopathologic review is required for patient eligibility and clear definitions of the determination of completeness of response have been established.

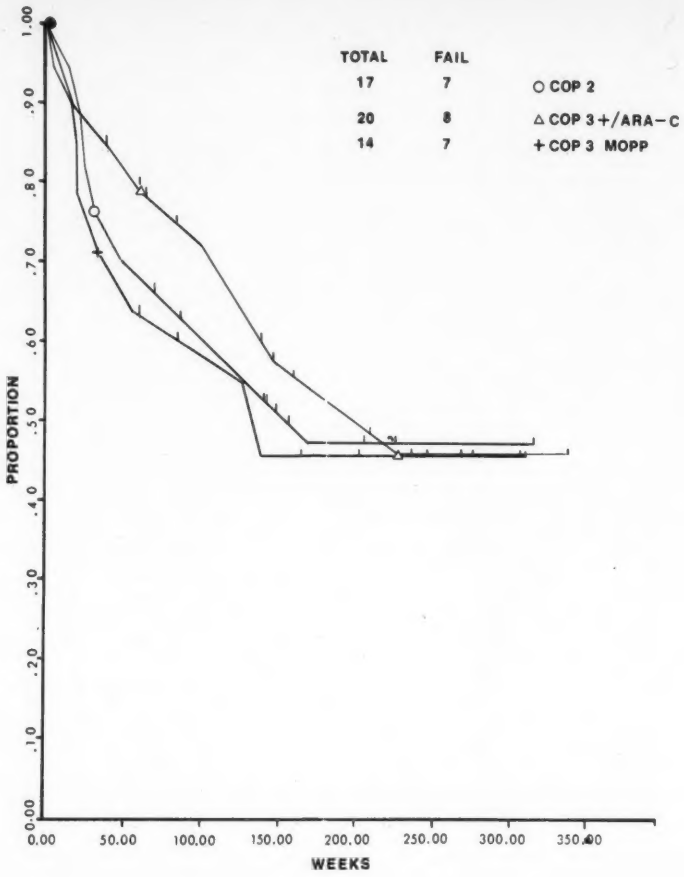

FIGURE 5.—Survival of NLPD patients in COP 2, COP 3 ± ARA-C, and COP 3-MOPP studies.

There remains significant room for improvement in the management of the less favorable DHL category of patients. We have done little to improve the management of the more favorable histologic categories (NLPD) beyond that afforded by single-agent chemotherapy.

LIST OF COMPOUNDS

Adriamycin: NSC-123127; CAS reg. No. 23214-92-8
Bleomycin: NSC-125066; CAS reg. No. 11056-06-7; [2,4'-bithiazole]-4-carboxylic acid, 2'-(2-aminoethyl)-, monohydrate
CHOP = cyclophosphamide, adriamycin, vincristine, and prednisone
COP = cyclophosphamide, vincristine, and prednisone
Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate
Cytosine arabinoside: NSC-63878; CAS reg. No. 69-74-9; cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride
HOP = adriamycin, vincristine, and prednisone
Mechlorethamine: NSC-762; CAS reg. No. 55-86-7; diethylamine, 2,2'-dichloro-*N*-methyl-, hydrochloride
MOPP = mechlorethamine, vincristine, prednisone, and procarbazine
OAP = vincristine, cytosine arabinoside, and prednisone
Prednisone: NSC-10023; CAS reg. No. 53-03-2; pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-
Procarbazine: NSC-77213; CAS reg. No. 491-88-3; *p*-toluamide, *N*-isopropyl-α-(2-methylhydrazino)-, monohydrochloride
Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1)

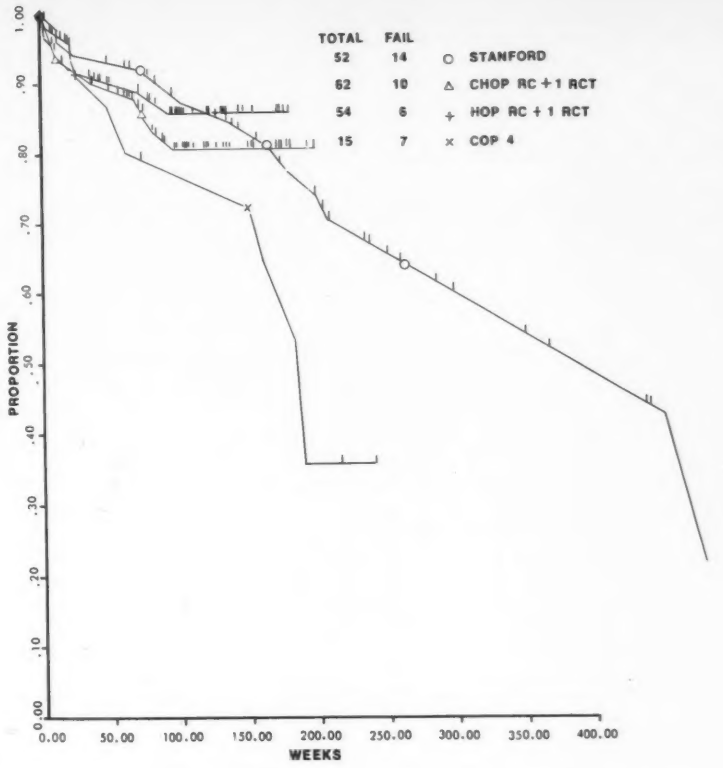

FIGURE 6.—Survival of NLPD patients in the COP 4, CHOP, HOP, and Stanford studies.

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Chemotherapy of Non-Hodgkin's Lymphomas: Eastern Cooperative Oncology Group Experience [1]

John M. Bennett,[2,*] Raymond E. Lenhard, Jr,[3] Ediz Ezdinli,[4] Gerhard J. Johnson,[5] Paul P. Carbone,[6] and Stuart J. Pocock [7]

SUMMARY

The addition of prednisone to the two-drug combination of cyclophosphamide and vincristine increases the number of complete remissions (CR). Patients who had CRs in at least two of the studies, EST 0168 and EST 3472, lived significantly longer than those who had partial remissions. In EST 0168, the survival time correlated strongly with the nodal pattern and cell type, confirming results of Rosenberg and co-workers. EST 1472 confirmed the activity of BCNU in lymphocytic lymphomas; when both agents are combined with prednisone, the induction potential of BCNU is equal to that of cyclophosphamide. In the histiocytic lymphomas, BCNU added to CVP increases the percentage of CRs but it does so at the expense of considerable toxicity. EST 0871 demonstrated that low-dose bleomycin and hexamethylmelamine are active agents in lymphoma and should be combined with other effective combinations in an attempt to improve the CR rate. Finally, our current studies demonstrate that the failure rate in the diffuse or unfavorable lymphomas is higher than that in the more favorable nodular forms.

[Cancer Treat Rep 61:1079–1083, 1977]

During the past decade, member institutions of ECOG have conducted nine phase II and III trials in patients with malignant lymphomas of the non-Hodgkin's type. This review will summarize the salient features of these studies, several of which are still ongoing active protocols.

The first study, undertaken jointly by the Acute Leukemia Group B and the ECOG (1), compared the single agent, cyclophosphamide, with both a high- and low-dose combination of cyclophosphamide, vincristine, and prednisone (CVP). The low-dose triad was calculated at two thirds of the high-dose program (table 1). The response rates are indicated in table 2. Significantly more complete remissions (CR) were achieved with the three-drug combinations (33%) than with the single agent (16%), but no differences were observed between patients with lymphocytic lymphoma and reticulum cell sarcoma. This study pre-dated review by the Pathology Panel for Lymphoma Trials. Maintenance therapy did not significantly affect the duration of remissions (49–100 days).

The next program, EST 0168, examined the role of prednisone in the therapy for lymphomas (2). The drug schedule (table 3) represented a compromise with the earlier study; it consisted of a low dose of cyclophosphamide and vincristine (CV) and a high dose of prednisone. Response rates and average survivals are given in table 4. More patients achieved CRs with CVP than with CV and the average survival was significantly higher for all patients who achieved a CR than for those who achieved a partial response (PR).

For the first time, the initial diagnostic slides were reviewed by a member of the Pathology Panel

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TABLE 1.—Remission induction therapy*

Drug (route)	Single agent (mg/kg/wk)	Combination treatment (mg/kg) High CVP	Combination treatment (mg/kg) Low CVP
Cyclophosphamide (iv)	15	15/wk	10/wk
Vincristine (iv)	--	0.025/wk	0.017/wk
Prednisone (oral)	—	1.0/day	0.67/day

*Treatment course = 6 wks; maintenance = methotrexate or no treatment.

TABLE 2.—Response by disease and therapy

Treatment	CR + PR (%) Non-Hodgkin's lymphoma	CR + PR (%) Reticulum cell sarcoma
Cyclophosphamide	43	45
High-dose CVP	100 ($P < 0.01$)	85 ($P < 0.05$)
Low-dose CVP	90	54

TABLE 3.—Remission induction therapy: EST 0168*

Drug	Group 1: CVP (mg/kg)	Group 2: CV (mg/kg)
Cyclophosphamide	10.0	10.0
Vincristine	0.017	0.017
Prednisone	1.0	—

*Treatment course = 8 wks; maintenance = 8 wks of CV or no treatment.

for Lymphoma Trials (Dr. Costan Berard). Seven percent of the cases were discarded because they failed to meet appropriate histologic criteria, ie, carcinoma, non-malignant, inadequate specimen, etc. Although response to treatment did not correlate with pathology, survival time was strongly related to both nodal pattern and cell type (table 5), confirming results of Rosenberg et al (5). Survival times decreased from the well-differentiated lymphocytic to the poorly differentiated histiocytic cell types ($P < 0.05$). Patients who had lesions with a nodular pattern had a longer survival with the exception of seven who had diffuse well-differentiated lymphocytic lymphoma.

Cyclic therapy with CV extended the duration of remissions by approximately 8 months (12.8 months in the treated group as compared to 4.8 months in the unmaintained group), regardless of the induction program. Survival differences were not apparent.

Detailed analysis of cell types, race, sex, and extent of disease did not reveal any correlation with the CR rate. CR was correlated only with the addition of prednisone to the CV schedule. Both duration of remission and survival correlated with CRs obtained from either induction regimen. The results of this study support the current emphasis on developing programs that increase CRs.

Two completed phase III trials, EST 1472 and EST 3472, have examined the role of the nitrosourea, BCNU, in non-Hodgkin's lymphomas. The regimens and detailed response data have been published recently (3). EST 1472 confirmed the activity of BCNU in lymphocytic lymphomas, both nodular and diffuse. The CRs seen with the combination of BCNU-prednisone versus cyclophosphamide-prednisone (CP) were 18% and 23%, respectively. Both regimens achieved CRs comparable to that obtained with the CV program of EST 0168, but these rates were inferior to that of the CVP program (38%). Approximately half of the patients who failed to achieve at least a PR obtained a successful induction with other programs, demonstrating lack of cross resistance for both BCNU and cyclophosphamide.

EST 3472 compared CP, CVP, and BCNU plus CVP (BCVP) in histiocytic and mixed cell lymphomas, both nodular and diffuse. Subsequently, the Pathology Panel for Lymphoma Clinical Trials (Drs. Costan Berard and Robert Hartsock) requested all slides for review. The final analysis of this study, chaired by Dr. Raymond E. Lenhard, Jr, was based primarily on patients whose diagnostic material was reviewed by the panel. Only patients ≥ 14 years old were eligible for study. The cycles were administered every 3 weeks for 6 months (nine cycles). The major goal of treatment was to achieve CR, and at the end of 6 months those patients in CR were followed without further therapy until relapse. At the end of nine cycles, patients who showed no change or had only PR with CP or CVP were escalated to the BCVP regimen. Of 225 patients in the study, 187 were considered eligible for evaluation. Of the non-eligible cases, seven were classified as "not lymphoma" by Pathology Panel review, six had no measurable disease, 13 had protocol violations, and 12 had rapid progression within the first few days of treatment. Of the 187 evaluable patients, 143 (76%) had Pathology Panel review; 117 patients (82%) had diffuse histiocytic or diffuse mixed cell lymphoma and only 26 (18%) had nodular lymphomas. The interpretations of the Pathology Panel and the pathologists at the contributing institutions did not agree in 34% of the slides. Most of these discrepancies were between histiocytic and mixed cell diagnoses.

TABLE 4.—Response rates and survival: EST 0168

Treatment	No. of patients treated	CR (%)	CR survival (mos)	PR (%)	PR survival (mos)
CVP	54	43	57	39	39
CV	59	17	50	53	30

TABLE 5.—Survival time with cell type and nodal pattern: EST 0168

	Median survival (yrs)*					
	Cell type					
Nodal pattern	Well-differentiated lymphocytic	Poorly differentiated lymphocytic	Mixed†	Histiocytic	Undifferentiated	Totals
Nodular	—	4.2 (20)	1.9 (5)	2.0 (2)	—	3.6 (27)
Diffuse	11.9 (7)	2.9 (19)	3.0 (7)	1.3 (24)	2.0 (14)	2.2 (71)
Totals	11.9 (7)	3.6 (39)	2.5 (12)	1.4 (26)	2.0 (14)	2.4 (98)

*Nos. in parentheses = No. of cases.
†Mixed = poorly differentiated + histiocytic.

A higher CR rate was recorded following both CVP and BCVP (34%) compared to the CP regimen (21%). These differences were not quite statistically significant at $P < 0.05$. Responses were evaluated at the end of 6 months of treatment and patients who had entered CR but had relapsed before this time were not included in the analyses. Of these 48 transient responses, eight were CRs and 40 were PRs. If these patients had been included in the analysis, the overall response rate would have risen from 44% to 70%.

Only two detailed subclassifications of the Pathology Panel, diffuse mixed and diffuse histiocytic, contained adequate numbers for statistical comparison. The response rate between these two cell types did not differ; however, there was a significant difference ($P = 0.01$) between the CR rate in nodular (50%) and diffuse (25%) nodal patterns.

In EST 3472 there was no positive correlation between the CR rate and the level of toxicity. More toxicity was not associated with a greater antitumor effect. In fact, the lowest CR rate (13%) was found in those patients reported to have the most severe toxicity regardless of the treatment group.

At the time of this report, 42 of the 63 patients in EST 3472 who achieved CRs have relapsed. The median duration of the CR was 40 weeks. Most patients have had a followup for > 1 year, and 62% have died. The estimated mean survival after CVP treatment is 118 weeks, which is significantly longer than 74 weeks after CP ($P = 0.05$) and 76 weeks after BCVP ($P = 0.07$). The estimated mean survival for the entire patient population is 86.7 weeks.

Patients with mixed cell histology had a significantly longer median survival than those with histiocytic histology. A comparison of all nodular lymph node patterns with those of diffuse lymphomas also demonstrated a better survival record for nodular pattern. In the crossover study (the administration of BCVP to those who had failed on CP or CVP) an additional 10% of patients entered CR. The only apparent reason for shorter survival in the four-drug treatment group was the excess toxicity. This factor was also apparent in patients who were not able to achieve a CR; these "non-responders" survived for a shorter period than those who were treated with CP or CVP.

Two new studies, EST 2474 and EST 3474, were launched in October 1974, taking advantage of the correlation of pathologic subtypes, including the apparent longer survivals of the nodular lymphomas and the data concerning chemotherapeutic responses from the previous programs. EST 2474 examines the value of moderate (CP) versus intensive (BCVP) therapy or a combination of cyclophosphamide, vincristine, prednisone, and procarbazine (COPP) (4) in favorable subtypes (nodular forms and diffuse well-differentiated lymphocytic type). Patients achieving CR are further randomized to 13 cycles (18 months) of BCVP or no treatment. The preliminary results of this study are summarized in table 6 and remain coded. Overall, 91% of pa-

TABLE 6.—EST 2474: remission induction for 3 regimens (coded); objective response by treatment

Response	No. responding (%) to—			
	CT-1	CT-2	CT-3	Totals
CR	11 (38)	13 (41)	13 (45)	37 (41)
PR	14	17	15	46 (51)
No change and progression	4	2	1	7 (8)
Totals	29	32	29	90 (100)

TABLE 7.—EST 3474: remission induction for 4 regimens (coded); objective response by treatment

Response	No. responding (%) to—				
	CT-1	CT-2	CT-3	CT-4	Totals
CR	18 (72)	11 (44)	11 (39)	7 (37)	47 (48)
PR	4 (16)	9 (36)	9 (32)	7 (37)	29 (30)
No change and progression	3	5	8	5	21 (22)
Totals	25	25	28	19	97 (100)

tients have achieved CRs and PRs and approximately half of them have obtained CRs.

In EST 3474, four different four-drug regimens are being employed in the unfavorable histologic subtypes: diffuse lymphocytic, mixed, and histiocytic forms. BCVP is compared to cyclophosphamide, vincristine, prednisone, and adriamycin (COPA), cyclophosphamide, vincristine, prednisone, and bleomycin (COPB), and the latter four drugs with the vincristine and bleomycin administered 2 weeks after cyclophosphamide and prednisone (CPOB). The maintenance program is identical to that used in EST 2474. The schemas and regimens of both EST 2474 and EST 3474 have been published elsewhere (3).

In contrast to the drugs compared in EST 2474, there appear to be some differences between the response rates of the four programs (table 7). Although the analysis of the data must be regarded as preliminary and is subject to revision after final pathology review and overall assessment by the drug study chairman, the regimen CT-1 clearly appears to produce more CRs at the expense of fewer PRs. Consistent with our previous studies, the percent of failures (no change and progression) is almost three times higher in unfavorable than in favorable lymphomas (22% versus 8%). The percent of CRs and PRs in both studies is comparable.

In addition to these phase III trials, the ECOG has conducted phase II programs with stage III and IV non-Hodgkin's lymphomas resistant to or progressive after more standard chemotherapeutic approaches. A randomized prospective protocol, EST 0871, compared a low-dose and high-dose weekly schedule of bleomycin (5 mg/m² versus 25 mg/m², respectively) with a second agent, hexamethylmelamine (HXM) (300 mg/m²/day orally). Patients who failed to respond to the low-dose bleomycin schedule were given the high-dose schedule after 4 weeks of treatment. All non-responders were crossed over to the other available agent.

Significant unfavorable patient characteristics included the following: 65% > 50 years old; disease present for > 1 year in 70%; prior treatment including radiation in 100%; and non-ambulatory performance status in 50%. Pulmonary toxicity was noted only with high-dose bleomycin and with HXM. Hematologic, gastrointestinal, and neurologic side effects (irritability and mental confusion) were common.

In most clinical trials the response rates with crossover treatment are lower than with initial treatment. In this study, with one important exception, crossover response rates were the same (table 8). The overall response rates (CR and PR) were 28% and no differences were seen between low-dose bleomycin, high-dose bleomycin, and HXM. There were no discernible differences between histologic subtypes, except that three of the four CRs occurred in patients with mixed or histiocytic lymphoma. Of

TABLE 8.—Responses for initial and crossover treatment: EST 0871

Histology	Low-dose bleomycin			High-dose bleomycin			HXM		
	CR	PR	NR	CR	PR	NR	CR	PR	NR
Lymphocytic	0	3	9	0	6	12	1	3	8
Mixed and histiocytic	0	3	11	1	7	16	2	2	14
Totals	0	6	20	1	13	28	3	5	22
% response		23			33			27	

extreme importance was the fact that, of 12 patients who failed to respond to low-dose bleomycin (total dose, 20–40 mg/m²), none responded to high-dose bleomycin (total dose, 100–200 mg/m²).

Sixty-one percent of the responses occurred within 4 weeks of initial treatment. The median dose to response was 13.7 mg/m² for low-dose bleomycin, 57.7 mg/m² for high-dose bleomycin, and 4 g/m² for HXM. With a few exceptions, most responses were of short duration (median = 6 weeks). Preliminary survival data indicate that patients who received high-dose bleomycin had worse survival than patients receiving either low-dose bleomycin or HXM.

The current phase II program, EST 1474, compares a low-dose daily schedule of bleomycin (1 mg sc for 4 weeks) with one of the epipodophyllin derivatives, VM-26 (100 mg/m²/week iv). Finally, EST 1475 compares the effectiveness of segmental and transdiaphragmatic extended field radiation followed by combination chemotherapy (CVP) in stage I and II non-Hodgkin's lymphoma. It would be premature to comment on the results of either of these two studies at this time.

LIST OF COMPOUNDS

Adriamycin: NSC-123127; CAS reg. No. 23214-92-8

BCNU: NSC-409962; CAS reg. No. 154-93-8; urea, 1,3-bis(2-chloroethyl)-1-nitroso-

Bleomycin: NSC-125066; CAS reg. No. 11056-06-7; [2,4'-bithiazole]-4-carboxylic acid, 2'-(2-aminoethyl)-, monohydrate

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate

Hexamethylmelamine: NSC-13875; CAS reg. No. 645-05-6

Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-

Prednisone: NSC-10023; CAS reg. No. 53-03-2; pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-

Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1)

VM-26: NSC-122819; 4'-demethylepipodophyllotoxin, 9-(4,6-*O*-2-thenylidene-β-D-glucopyranoside)

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BCNU With and Without Cyclophosphamide, Vincristine, and Prednisone (COP) and Cycle-Active Therapy in Non-Hodgkin's Lymphoma [1]

John R. Durant,[2,*] Richard A. Gams,[3] Alfred A. Bartolucci,[4] and Ronald F. Dorfman [5,6]

SUMMARY

Two hundred and ninety-eight evaluable patients with non-Hodgkin's lymphoma were stratified according to histology, treated with either BCNU, cyclophosphamide, Oncovin (vincristine), and prednisone (BCOP) or cyclophosphamide, Oncovin (vincristine), and prednisone (COP), and evaluated at 3 months. Those with a good partial (PR) or complete response (CR) were then separated and randomized to be treated with either cycle-active therapy (methotrexate, cytosine arabinoside, and 6-thioguanine) or more induction therapy with COP or BCOP. Patients not achieving a good PR at 3 months received cycle-active therapy. The results indicate (*a*) that there is a significant advantage for good over poor histologies with regard to good PRs at 3 months; (*b*) that the addition of cycle-active therapy (as administered in this study) is of advantage when the tumor has been significantly reduced only for patients receiving COP induction; and (*c*) that BCOP has an advantage over COP in diffuse histiocytic lymphoma where the percentage of CRs, their durability, and subsequent survival are superior for patients treated with BCOP. Since this lymphoma accounts for about 25% of all non-Hodgkin's lymphoma patients, this regimen represents a useful tool for the chemotherapist.

[Cancer Treat Rep 61:1085–1096, 1977]

The non-Hodgkin's lymphomas are now recognized as a heterogenous group of disorders with varying prognoses. The classification of these disorders described by Rappaport (1) and Jones et al (2) has led to a clinically useful grouping of good- and poor-risk patients.

The combination of cyclophosphamide, Oncovin (vincristine), and prednisone (COP), originally described by Luce et al (3), is widely used in the management of non-Hodgkin's lymphomas. Since complete remissions (CR) are usually obtained in less than half the patients and the remissions are frequentiy short-lived, such management is considered largely palliative. Consequently, many investigators, including the Southeastern Cancer Study Group have been exploring alternatives to the standard COP regimen.

Because of reported synergism between nitrosoureas and cyclophosphamide in animal tumor systems, the Southeastern Group has been using combinations of BCNU and cyclophosphamide in a variety of disorders. In one of these studies the combination of BCNU, cyclophosphamide, Oncovin (vincristine), and prednisone (BCOP) was used in a large group of patients with diffuse histiocytic lymphoma in a phase II study (4). In this study, the CR rate (50%) and median survival of nearly 2 years in previously untreated patients achieving CR suggested an improvement over the historical experience with COP. Consequently, it was thought advisable to carry out a phase III randomized comparison of COP and BCOP, not only in diffuse histiocytic lymphoma but also in the other categories of non-Hodgkin's lymphomas.

[1] Supported by Public Health Service grants CA-19657 and CA-19892 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

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[6] We wish to thank Karen L. Rose and Kay W. Bienke at the Southeastern Cancer Study Group Regional Statistical Office who assisted in the patient analysis.

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A further consideration in the design of the present study was the growing knowledge concerning tumor cell kinetics. It is now well recognized that bulky tumor has a low growth fraction. Consequently, patients initially presenting with a large amount of disease might be expected to respond better to regimens such as BCOP or COP which are relatively non-cell-cycle specific. Following reduction in the tumor burden in animals and man (5), the tumor growth fraction normally increases significantly. At this point, the introduction of cell-cycle-specific agents, particularly those active in the synthetic phase of the cell cycle, might further reduce the number of tumor cells and improve the extent and duration of remission.

With these considerations in mind, the present study was developed with the following objectives:

(1) To determine whether the addition of BCNU to COP resulted in an improvement in the remission rate and survival in all categories of non-Hodgkin's lymphoma.
(2) To determine whether the introduction of cell-cycle-specific agents in a consolidation phase would convert PRs to CRs or increase the remission duration and survival in CRs.
(3) To study the influence of histologic categories of non-Hodgkin's lymphoma on remission rate, remission duration, and survival.

MATERIALS AND METHODS

All member institutions of the Southeastern Group participated in this study, which began on January 18, 1973. At the time of this analysis 495 patients have been entered in the study; of these, 81 were considered ineligible primarily because of incorrect histologic diagnosis or inability of the pathology referee to classify the lymphoma. Of 334 eligible patients who have completed treatment, 298 were considered evaluable at 6 months. Reasons for inevaluability include major protocol violations (28 patients) and patients lost to followup (eight patients).

Patients were considered eligible for the study if they had a biopsy diagnosis of non-Hodgkin's lymphoma confirmed by the pathology referees for the Southeastern Group and members of the Pathology Repository Committee of the Lymphoma Task Force. Excluded from the study were patients with stage I disease, patients considered to have chronic lymphocytic leukemia as defined by standard criteria, patients without measurable lesions, and patients who had had major prior therapy defined as radiation therapy > 3000 rads within three or more anatomic areas and/or demonstrated resistance to one or more of the chemotherapeutic agents in the combination-treatment regimens. Clinical data on all patients were reviewed independently by the Project Co-Chairmen (John R. Durant and Richard A. Gams) plus one independent reviewer.

Patients were stratified before induction therapy according to the Rappaport classification based on the decision of each institution's own pathologist. The patients were restratified at the time of consolidation therapy according to the Rappaport classification assigned by the pathology referees.

Staging was accomplished by obtaining a detailed history, physical examination, chest roentgenogram, bone marrow biopsy, lymphangiogram, and other studies which were clinically indicated. Liver biopsy was not performed routinely. The Ann Arbor classification for Hodgkin's disease was adapted for use in the non-Hodgkin's lymphomas. Scanning with gallium and B-mode ultrasonography often was carried out but was not considered in the staging or evaluation.

The study design and treatment regimens are shown in figure 1. All patients were randomized initially between 3 months' induction therapy with BCOP versus 3 months' induction therapy with COP. After 3 months' induction, all patients who achieved a CR or PR were then randomized to continued induction therapy with BCOP or COP or 3 months of cycle-active therapy with methotrexate, cytosine arabinoside (The Upjohn Co, Kalamazoo, Mich), and 6-thioguanine. Patients achieving less than a good PR at 3 months were crossed over in a nonrandom fashion to the cycle-active arm of the study. Dosage modifications were made as indicated clinically in an attempt to produce some reduction in the granulocyte or platelet counts. Vincristine was discontinued for disabling paresthesias. Prednisone was stopped if uncontrollable complications attributed to this agent developed.

Remission status was determined according to Southeastern Group criteria as either CR (disappearance of all signs and symptoms of disease) or good PR (disappearance of all symptoms and a decrease of ≥ 50% in all measurable parameters of disease without the appearance of new lesions). Evaluation after the induction therapy was carried out 2 weeks after the sixth targeted dose of vincristine and 2 weeks after the last doses of cytosine arabinoside and 6-thioguanine for the consolidation part of the study. Although extensive restaging was not carried out, the protocol directed that all study results abnormal at the start of the study be repeated at its completion.

Toxicity was evaluated according to standard Southeastern Group criteria (6). Survival curves were calculated using the method of Kaplan and Meier (7), and the method of Gehan (8) was used for

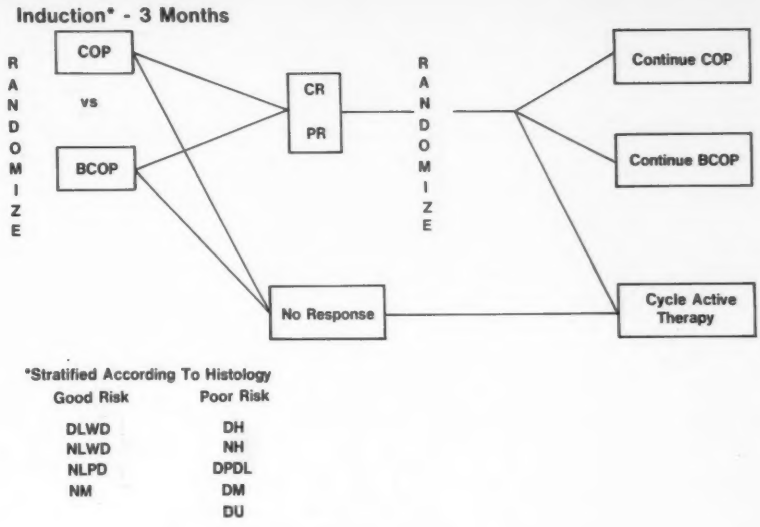

FIGURE 1.—Non-Hodgkin's lymphoma: scheme for therapy.

the comparison of the survival curves. Chi-square statistics were used to test the difference in the remission rates.

RESULTS

Despite the accession of nearly 500 cases since January 1973 and a review of 406 of these by the pathology referee, conclusions must be preliminary. Not only does this study have four different treatment regimens, it has two decision points and nine histologic stratifications. Thus, data frequently are too preliminary to make valid statistical comparisons. However, some trends appear to be of great interest and will be reported.

First, the importance of histologic review is obvious. In 205 of 406 cases (48%) the referee disagreed with the local pathologist concerning the specific Rappaport classification. If only changes from the broad categories of good and poor risk are considered, there was disagreement in 56 of 406 cases (14%). In the case of diffuse histiocytic lymphoma, where we believe special designation is important, the referee made a different diagnosis in 32 cases. These data confirm the experience of the Southwest Oncology Group in a much smaller number of cases (9).

The present data represent results in completed cases, a small minority of which have not yet been histologically reviewed. We have divided cases into good- and poor-risk categories as follows. *Good risk*—(1) diffuse lymphocytic, well-differentiated; (2) nodular lymphocytic, well-differentiated; (3) nodular lymphocytic, poorly differentiated; and (4) nodular mixed. *Poor risk*—(1) nodular histiocytic; (2) diffuse histiocytic; (3) diffuse lymphocytic, poorly differentiated; (4) diffuse mixed; and (5) diffuse undifferentiated.

This distinction by histologic classification into good- and poor-risk categories appears to be very important. Table 1 shows that the response rate for good histologies is significantly greater than for poor histologies at 3 months. This is due to a better good PR rate in the good-risk histologies because the CR rate in both groups was the same. Good-risk patients originally treated with either COP or BCOP survived significantly longer than similar poor-risk patients (fig 2), but the duration of these remissions (fig 3) was not different whether all remissions or only CRs were considered. Thus, it appears that histologic classification has an important effect on response rates and survival without influencing duration of response, suggesting again that the biology of the disease must be considered when assessing the value of any treatment. Furthermore, although the response and duration of remission of good-risk histologies to COP and BCOP were the same, subsequent survival was very different, regardless of the maintenance therapy, suggesting a value for BCNU in this group of patients.

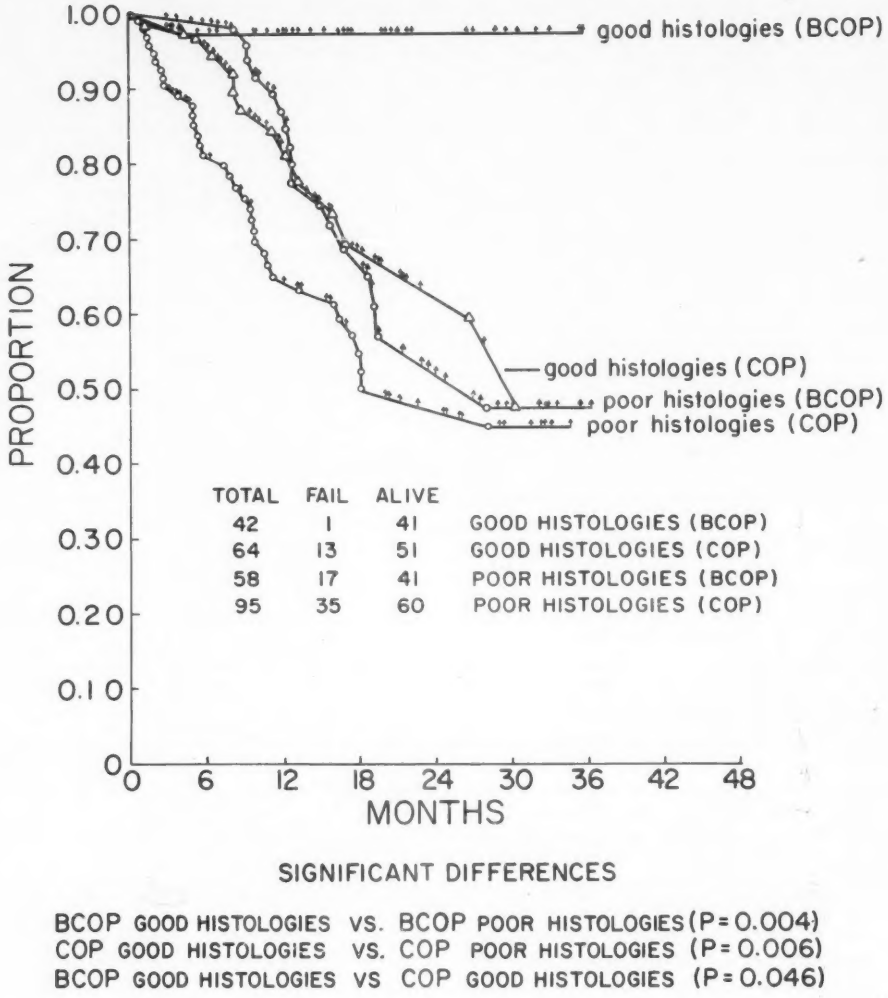

FIGURE 2.—Non-Hodgkin's lymphoma: survival among responders (3 months' induction). CR and good PR according to histologic treatment.

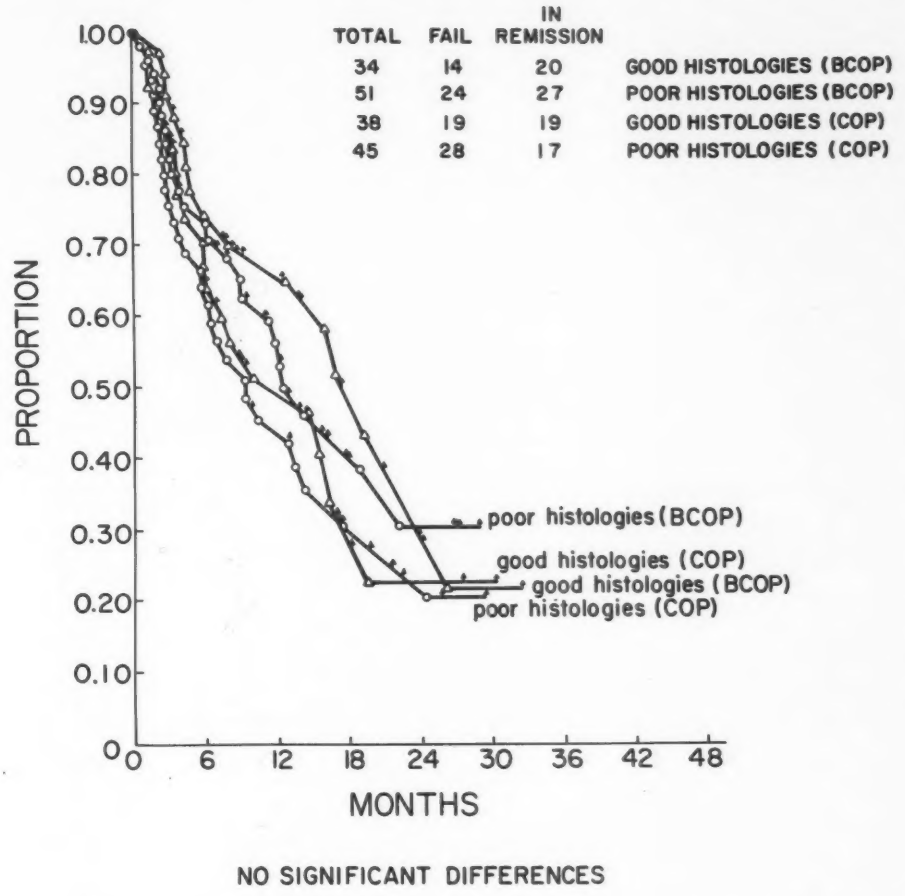

FIGURE 3.—Non-Hodgkin's lymphoma: duration of remission after COP and BCOP therapy by histology (3 months' induction).

TABLE 1.—Response rates of non-Hodgkin's lymphoma according to histology

Histology	No. of CRs/ No. treated	No. of CRs + good PRs/No. treated
Good	39/115 (34%)	94/115 (81%)
		$P = < 0.005$
Poor	59/185 (32%)	118/185 (64%)

COP With and Without BCNU

The response rates at 3 months to standard COP and BCOP were essentially identical. About one third of all patients, regardless of histology, achieved a CR. As noted above, although significantly more good- than poor-risk patients achieved a good PR (one half of the good-risk patients versus one third of the poor-risk patients, $P < 0.005$), the good PR rates to BCOP and COP at 3 months and the death rate within each risk category were virtually identical.

At 6 months, however, an advantage which is not yet statistically significant (table 2) begins to appear for BCOP in the poor- but not the good-risk patients. Forty-one percent of good-risk patients treated with BCOP and 36% treated with COP achieved CRs. On the other hand, 28% of the poor-risk patients treated with BCOP but only 18% of those receiving COP achieved CRs. When these results are analyzed according to histology, this advantage for BCOP appears only in the diffuse histiocytic category. Ten of 29 patients (34%) with diffuse histiocytic lymphoma initially started on BCOP and either maintained on it or dropped because of failure to respond, achieved a CR at 6 months, whereas only three of 23 similar patients (13%) treated with COP did so. Although this is not yet significant by chi-square analysis, the trend is obvious. On the other hand, there is absolutely no difference between BCOP and COP at 6 months for categories other than diffuse histiocytic (six CRs among 28 patients, 21%, versus eight CRs among 39 patients, 21%). Thus, the addition of BCNU to COP probably improves the response rate in non-Hodgkin's lymphoma only in patients with diffuse histiocytic lymphoma. This advantage carries over in duration of remission. Figure 4 shows this for those achieving CR and good PR at 6 months. Survival was improved only in those achieving CRs, as shown in figure 5. COP is omitted because so few patients had a CR (three of 23 patients) at 6 months. Survival of patients with CR in our previous study is also shown, and although the probability of surviving with diffuse histiocytic lymphoma after a CR is 20% better at 33 months in our current study, this difference is not significant. Patients treated with BCOP perform better than COP-treated patients with diffuse histiocytic lymphoma, primarily because so few COP patients maintain a CR at 6 months. Toxic effects are essentially similar for both COP and BCOP.

Cycle-Active Therapy

Cycle-active therapy as used in this study was of advantage only for patients induced with COP. Figure 6 shows that for all histologies achieving at least a good PR with COP, switching to cycle-active therapy provides an advantage, not yet significant for remission duration. Figure 7 shows, however, a statistically significant survival advantage ($P = 0.032$) over the first 2 years of followup for patients induced with COP and switched to cycle-active therapy. No such advantages are evident for those initially treated with BCOP.

One patient failing non-cycle-active induction and switched to cycle-active therapy achieved CR, and two additional patients (out of 28) not achieving at least a good PR during induction therapy achieved a good PR. All of these responders had diffuse histologies.

Among poor-risk histologies, non-cycle-active therapy maintained a 65% CR rate (13 CRs among 20 patients). Cycle-active therapy also maintained approximately the same percentage (60%, 15 CRs among 25 patients), but converted fewer PRs to CRs (13 PRs to CRs among 28 patients, 46%, versus

TABLE 2.—CRs in non-Hodgkin's lymphoma: BCOP vs COP according to histology

	No. of CRs/ No. treated	No. of CRs/No. treated (diffuse histiocytic)	No. of CRs/No. treated (poor risk, non-diffuse histiocytic)
BCOP			
Good risk	11/27 (42%)		
Poor risk	16/57 (28%)	10/29 (34%)	6/28 (21%)
COP			
Good risk	10/28 (36%)		
Poor risk	11/62 (18%)	3/23 (13%)	8/39 (21%)

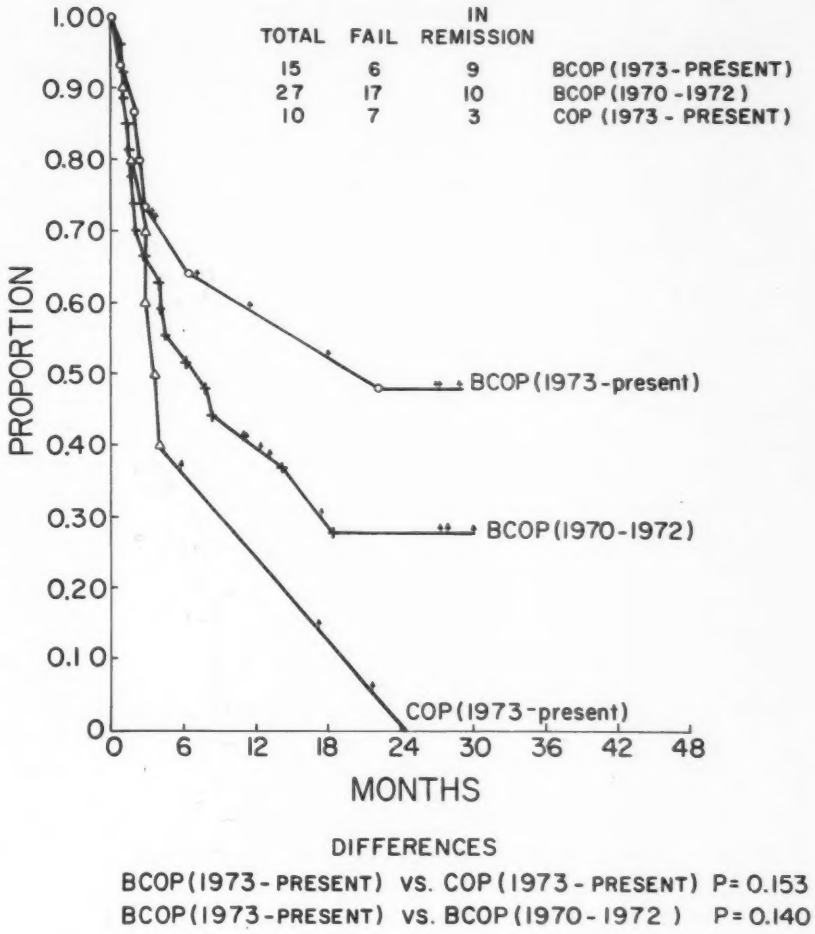

FIGURE 4.—Diffuse histiocytic lymphoma: duration of remission (CR and good PR) according to therapy.

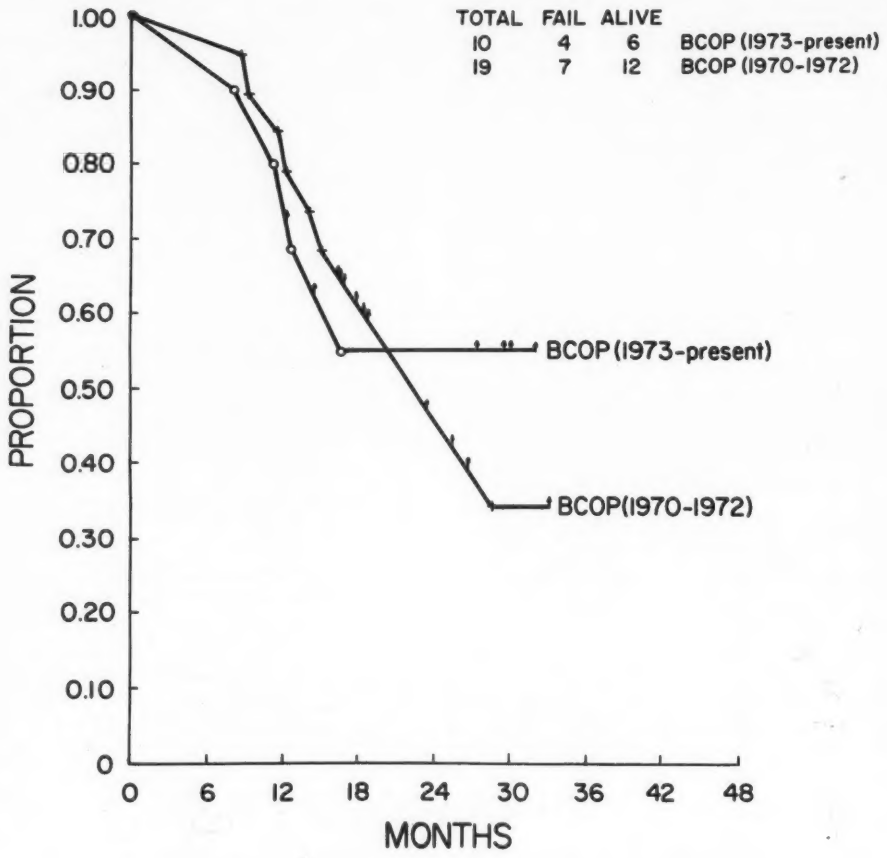

FIGURE 5.—Diffuse histiocytic lymphoma: survival among CRs according to therapy.

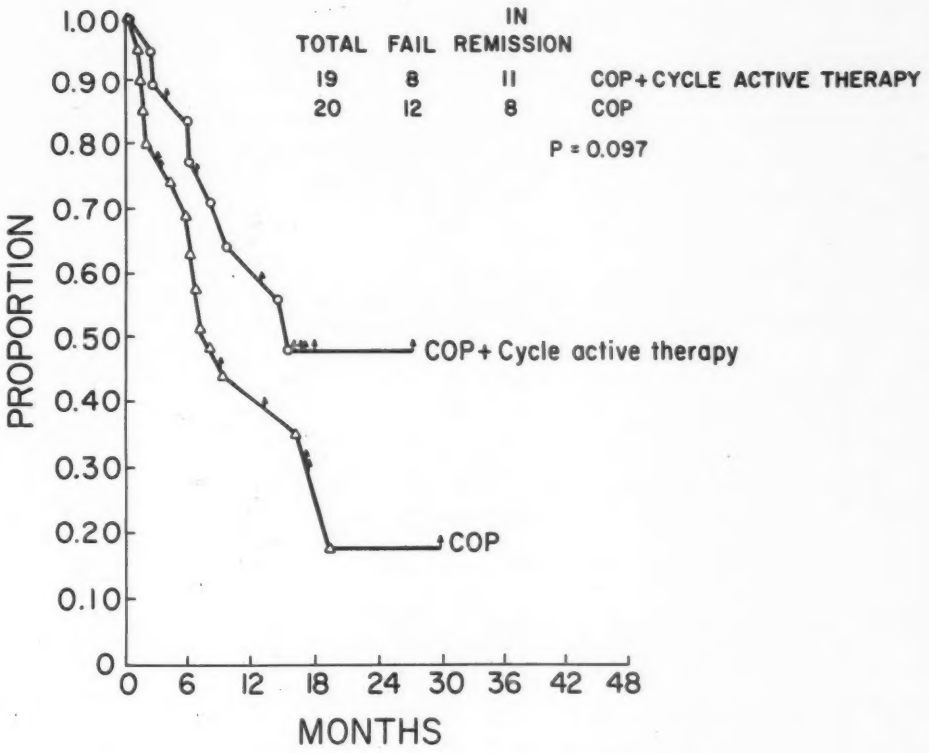

FIGURE 6.—Non-Hodgkin's lymphoma: duration of remission by therapy.

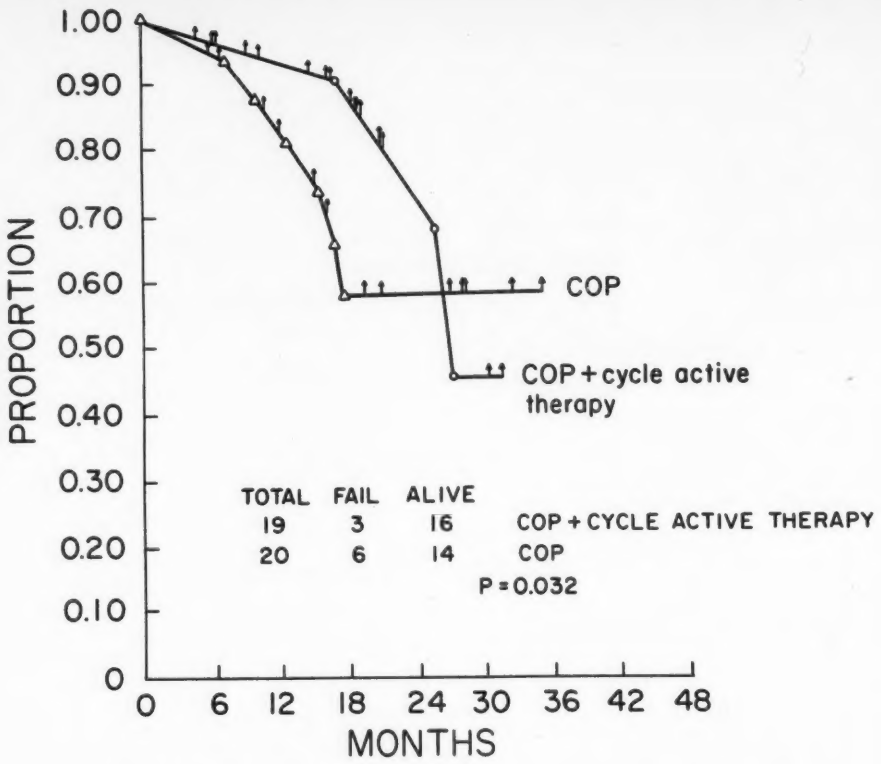

FIGURE 7.—Non-Hodgkin's lymphoma: survival among responders according to therapy.

three PRs to CRs among 13 patients, 23%). This difference is not significant. Remission duration and survival of 15 poor-risk patients with CR maintained on non-cycle-active therapy and 13 similar patients maintained on cycle-active therapy as yet show no significant results, but the numbers of patients in these categories are very small.

In the good-risk patients, cycle-active therapy again shows no advantage. Indeed, it may be deleterious because 94% of the good-risk patients with CRs (15 of 16) maintained on non-cycle-active therapy retained their CR at 6 months, whereas only 61% of the patients (eight of 13) maintained on cycle-active therapy did so. This difference, although large, is not yet statistically significant. A minority of good-risk patients with a good PR on induction with non-cycle-active therapy achieved a CR on either therapy (six CRs among 17 patients, 35%, versus four CRs among 21 patients, 19%). Followup is too short to make meaningful comparisons of duration of remission and survival for this category of patient.

Accordingly, we conclude that this program of cycle-active therapy administered until hematologic toxicity occurs offers little advantage in the management of either good- or poor-risk patients unless COP is the inducing regimen. It may be deleterious for remission maintenance for good-risk patients.

DISCUSSION

COP is the standard of comparison for the management of non-Hodgkin's lymphoma. It falls far short of the ideal. There appears to be no advantage to its use compared to continuous, single-drug, alkylating-agent therapy in good-risk patients with advanced-stage disease as to remission rate, duration of remission, and survival (10). Luce et al (3) reported that for reticulum cell sarcoma, which includes most poor-risk patients, the remissions induced are short-lived and maintenance is of no value.

The data derived from our studies confirm the relative ineffectiveness of COP. As far as good-risk

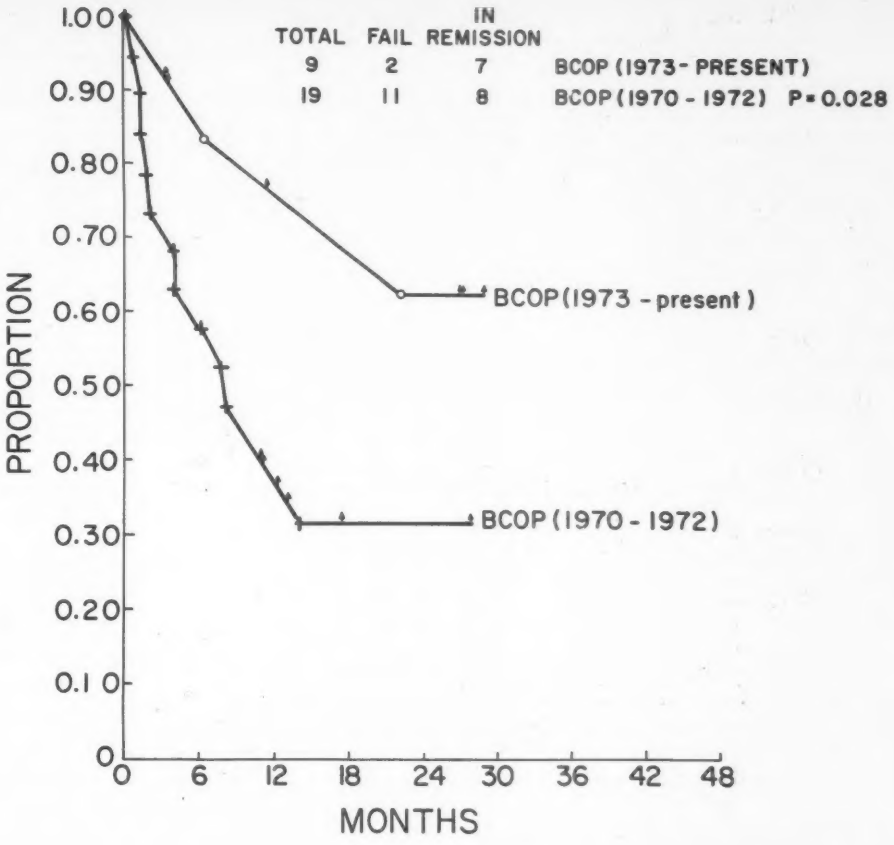

FIGURE 8.—Diffuse histiocytic lymphoma: duration among CRs according to period of therapy.

patients are concerned, it appears that virtually any treatment is satisfactory. As noted before, the Stanford group has evidence that single agents are as effective as the more complicated and toxic programs. For poor-risk patients, particularly those with diffuse histiocytic lymphoma, although approximately 60% will respond to COP with at least a good PR by 3 months, only 17% retain this status at 6 months. In our experience with diffuse histiocytic lymphoma, the vast majority of these relapses occur within the following few months (median duration, 3 months). Our attempts to improve these results have met with partial success. We recently reported (4) that 6 months of BCOP in previously untreated diffuse histiocytic lymphoma produced a 50% CR rate (14 CRs among 28 patients) and a 75% CR plus good PR rate (21 CRs + good PRs among 28 patients) with approximately 32% of the CRs expected to persist for > 2 years. It has been suggested that such prolonged remissions may be equivalent to a "cure" (11). The current study making a direct comparison of COP with BCOP in diffuse histiocytic lymphoma did not produce as high a response rate (41%) but did produce 34% CRs. As noted, these remissions are durable, 62% probability of remaining in CR at 32 months, and are superior to those previously reported by our group (fig 8). Whether these results are equivalent to those achieved by adding adriamycin to COP (CHOP) (12) is a matter for speculation. It would appear that for diffuse histiocytic lymphoma a direct comparison of BCOP, CHOP, and a combination of the two would be useful.

A major objective in this study was to test the hypothesis that the addition of cycle-active therapy might be effective after reduction of tumor. As used in this study, this strategy offers an advantage only for COP-treated patients. It may be noted that

Berd et al (13) have reported that cycle-active therapy using methotrexate at much higher doses with citrovorum factor rescue and cytosine arabinoside by another schedule have produced impressive long-term results in a small number of patients also receiving cyclophosphamide and vincristine but not prednisone.

The dosages and schedules of methotrexate, cytosine arabinoside, and 6-thioguanine used in this study have produced therapeutic responses in acute myelogenous leukemia and solid tumors. The regimen produced significant toxicity in our patients. Nevertheless, in this study a regimen which is applicable to outpatient management offered no advantage over continuing non-cycle-active therapy with BCOP, a treatment which is far more convenient.

Finally, this study provides considerable data concerning the value of a histologic separation into good- and poor-risk categories. Since there was often disagreement between the referring pathologists and the referees concerning this distinction, a pathologic review is essential, especially if treatment decisions will depend upon histologic classification. The major difference between the two risk categories is not in the likelihood of achievement of CR but rather in the percentage of patients achieving good PRs and in the survival of the responders. However, the survival advantage is not due to duration of remission but to the natural history of the disease. Furthermore, it appears that a further separation of poor-risk histologies into "diffuse histiocytic" and "other lymphomas" may be of value. If we separate poor-risk histologies in this way, there is no difference between COP and BCOP or good or poor histologies except for diffuse histiocytic. The chance for CR, its duration, and subsequent survival are superior for diffuse histiocytic lymphoma treated with BCOP versus diffuse histiocytic treated with COP, although the numbers are yet too small for valid statistical conclusion.

LIST OF COMPOUNDS

BCNU: NSC-409962; CAS reg. No. 154-93-8; urea, 1,3-bis(2-chloroethyl)-1-nitroso-

BCOP: BCNU, cyclophosphamide, Oncovin (vincristine), and prednisone

COP: cyclophosphamide, Oncovin (vincristine), and prednisone

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate

Cytosine arabinoside: NSC-63878; CAS reg. No. 69-74-9; cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride

Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-

Prednisone: NSC-10023; CAS reg. No. 53-03-2; pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-

6-Thioguanine: NSC-752; CAS reg. No. 1832-72-0; purine-6-thiol, 2-amino-

Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1)

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Overview of Four Clinical Studies of Chemotherapy for Stage III and IV Non-Hodgkin's Lymphomas by the Cancer and Leukemia Group B[1,2]

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SUMMARY

This paper presents an overview of four Cancer and Leukemia Group B studies in 1266 patients with stage III–IV non-Hodgkin's lymphoma. The cases were analyzed across protocols; the major prognostic determinants were prior chemotherapy, age, and histology. The four studies proved that cyclophosphamide maintenance was superior to no maintenance even after prolonged intensive induction chemotherapy. Furthermore, the reinforcement program of monthly pulse doses of vincristine and prednisone, whose value was established in the treatment of acute leukemia, led to highly significant improvement in remission duration and survival. Other facets of the chemotherapy programs are still being subjected to analysis, but this report sets out some preliminary conclusions.

[Cancer Treat Rep 61:1097–1107, 1977]

Over the past 8 years the CALGB has carried out four major studies of chemotherapy in 1266 patients with non-Hodgkin's lymphomas. All four were first-line studies examining combination chemotherapy in stage III–IV patients and the patient populations were therefore fairly comparable, allowing us to pool some of the data in order to examine prognostic factors.

All four protocols stratified the patients according to the histologic classification of lymphosarcoma (lymphocytic lymphoma) or reticulum cell sarcoma but excluded giant follicular lymphomas. As the impact of the Rappaport classification became clear (1,2), we found it necessary to reclassify the histologic material of the study populations and we accomplished this in 813 of 1266 cases. Lost material or a heavy workload at the local pathology departments were the main reasons for the incompleteness of the reclassification.

The patient characteristics of the four study populations (table 1) are similar except for prior chemotherapy which differed in the eligibility criteria of the protocols. When analyzed across the studies, patients who had received chemotherapy before the protocol began were found to have a lower frequency of remission and a shorter median survival than patients not previously treated with chemotherapy (table 2). For this reason, the small group of patients with prior chemotherapy will be excluded from subsequent analyses.

Sex and previous radiotherapy had no prognostic influence, but, as shown in figure 1, age was a major determinant. The poorer prognosis for older patients is not surprising, but the poorer prognosis in the younger group (as compared to the middle-aged) seems to indicate a more aggressive type of disease. Because the age distribution in the study groups was equal, all age groups are included in the subsequent analyses.

The pathologic subclassification was of major

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[2]This study was performed by the Cancer and Leukemia Group B (CALGB; formerly known as Acute Leukemia Group B).

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TABLE 1.—Patient characteristics in 4 CALGB studies in stage III and IV lymphoma

Characteristic	Study			
	6703	6810	7051	7253*
No. of patients (% men)	109 (63)	342 (62)	368 (57)	447 (57)
% of patients with—				
No prior treatment	78	62	63	69
Prior radiotherapy	22	14	22	24
Prior chemotherapy (± prior radiotherapy)	0	23	11	5
% of patients—				
< 35 yrs	6	15	16	13
35–59 yrs	48	47	43	43
> 60 yrs	46	38	41	44
% of patients with histology of—				
Old classification				
Lymphocytic lymphoma	59	57	51	49
Reticulum cell sarcoma	41	43	49	51
Rappaport classification†				
NLWD	8	5	7	0
DLWD	8	14	11	14
NLPD	20	15	9	0
DLPD	13	22	27	30
NM	10	7	5	0
DM	4	7	6	12
NH	2	2	2	0
DH	33	27	32	40
DU	2	1	1	4
Favorable (NLWD, DLWD, NLPD, NM)	44	42	32	14
Unfavorable (DLPD, DM, NH, DH, DU)	56	58	68	86

*Patients with nodular lymphomas were excluded from protocol 7253.
†*See* text for explanation of histologic abbreviations.

TABLE 2.—Effect of previous chemotherapy on frequency of remission and survival

	Response*											
	Lymphocytic lymphoma			Reticulum cell sarcoma			Rappaport favorable			Rappaport unfavorable		
	No.†	%CR	%PR	No.†	%CR	%PR	No.†	%CR	%PR	No.†	%CR	%PR
No prior chemotherapy	573	46	39	524	40	33	182	42	40	528	45	35
Prior chemotherapy	80	39	35	63	25	33	29	38	34	57	40	26
	Median survival (mos)											
No prior chemotherapy	31.0			8.5			37.6			11.7		
Prior chemotherapy	12.1			6.9			15.0			8.5		

*CR is defined as complete disappearance of all lesions and objective and subjective evidence of active disease; PR is defined as ≥ 50% regression of all measurable disease and improvement in symptoms.
†Total No. of patients.

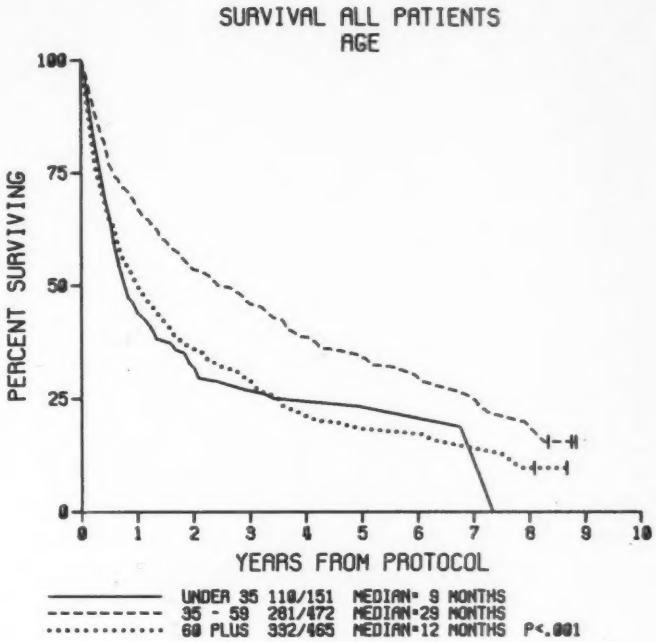

FIGURE 1.—Influence of age on survival of all patients not previously treated with chemotherapy.

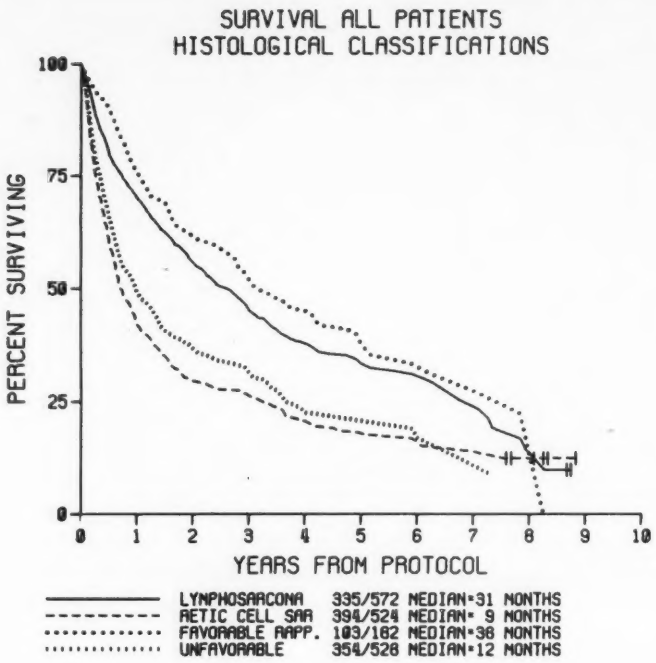

FIGURE 2.—Influence of histology on survival of all patients not previously treated with chemotherapy.

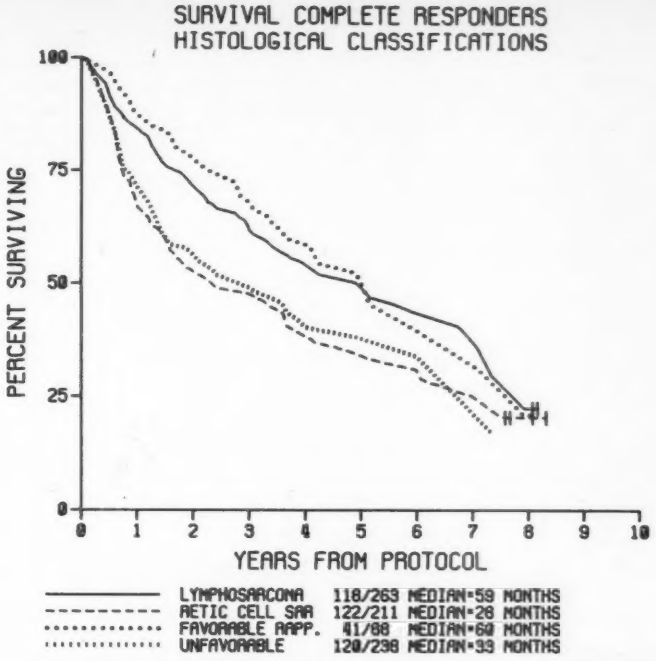

FIGURE 3.—Influence of histology on survival of patients achieving CR (patients with prior chemotherapy excluded).

prognostic importance. Table 1 shows the relative distribution for lymphosarcoma (lymphocytic lymphoma) and reticulum cell sarcoma and for the various subtypes according to the Rappaport classification. The groups nodular lymphocytic well-differentiated (NLWD), diffuse lymphocytic well-differentiated (DLWD), nodular lymphocytic poorly differentiated (NLPD), and nodular mixed (NM) are merged into the "favorable" category and diffuse lymphocytic poorly differentiated (DLPD), diffuse mixed (DM), nodular histiocytic (NH), diffuse histiocytic (DH), and diffuse undifferentiated (DU) into the "unfavorable" category in subsequent tables and figures. The reclassification showed that the lymphosarcoma group mainly contained DLWD (22.2%), NLPD (9.8%), and DLPD (45.9%), while the reticulum cell sarcoma group mainly became DM (11.4%) and DH (71.6%).

Table 3 demonstrates the marked variation in median survival according to pathologic subgroup; survival varies from around 50 months for the well-differentiated lymphocytic category down to around 7 months in the histiocytic lymphomas. The difference in survival is also clear when we compare the merged groups of favorable versus unfavorable categories. Both table 3 and figure 2 show that survival of our lymphocytic lymphoma group is comparable to that of the favorable histologies, and our reticulum cell sarcoma group is comparable to that of the unfavorable histologies.

Histology had less influence on the frequency of remission (table 4). However, comparison of figure 2 and figure 3 demonstrates the improved survival of those patients who obtained complete remission (CR) during the chemotherapy, and it shows that, even for this group of patients, the histologic subclassification retains its prognostic value.

Accordingly, the results of the four studies have been analyzed again, and while a detailed description will be published elsewhere (separately for each protocol), an overview will be presented here.

ALB 6703, initiated in 1967 and chaired by R. McIntyre, was built on a previous study in which the combination of vincristine (VCR), prednisone (PRED), and cyclophosphamide (CYT) had been proven superior to CYT alone (3).

In pilot studies, streptonigrin (SN) had shown promising results in lymphoma patients, and the study then examined whether improved results could be obtained using VCR + PRED + SN (VPS) as compared to VCR + PRED + CYT (VPC). Furthermore, the combination of VCR + PRED (VP) was introduced as a third regimen (fig 4).

Following 6 weeks of this induction therapy, the patients were randomized to maintenance therapy,

TABLE 3.—Influence of histology on frequency and duration of remission and on survival in patients not previously treated with chemotherapy

Histology	No. of patients	% CR	Median duration of remission (mos)	Median survival from onset of protocol (mos)
Lymphocytic lymphoma	573	46	25.3	31.0
Reticulum cell sarcoma	524	40	15.6	8.5
Rappaport classification				
NLWD	24	63	9.5	67.4
DLWD	88	47	20.7	43.0
NLPD	44	52	12.5	32.0
DLPD	186	49	17.0	18.0
NM	26	35	10.0	17.7
DM	61	46	23.9	19.1
NH	9	56	13.5	5.3
DH	253	42	13.0	8.0
DU	19	42	20.3	6.3
Favorable*	182	48	22.2	37.6
Unfavorable*	528	45	18.6	11.7

**See* table 1.

TABLE 4.—Frequency of best response throughout study in 4 CALGB protocols in patients not previously treated with chemotherapy

Study	Drugs*	Lymphocytic lymphoma			Reticulum cell sarcoma			Favorable			Unfavorable		
		No.†	%CR	%PR	No.†	%CR	%PR	No.†	%CR	%PR	No.†	%CR	%CR
6703‡	VPS	16	44	56	17	24	29	4	25	75	5	0	60
	VPC	24	8	63	16	31	31	5	20	80	8	13	63
	VP	24	17	67	12	8	67	9	22	78	8	13	75
6810	Combination VCR + SN + CYT + PRED	49	41	29	38	45	21	18	56	22	27	52	19
	Sequential VCR + SN + CYT + PRED	46	46	35	35	45	17	20	50	35	22	55	23
	VP → CYT	53	47	36	38	47	32	16	50	31	23	43	35
7051	Low VCR	78	63	28	75	31	35	29	59	31	63	48	33
	High VCR	81	49	35	81	47	30	33	58	30	64	50	31
7253	VP	56	46	43	60	33	38	15	40	47	83	40	39
	VPB	48	54	33	50	34	36	13	38	46	71	48	31
	VPS	48	31	54	45	49	38	9	22	67	71	42	39
	VPBS	50	56	32	57	53	33	11	64	36	79	52	33

**See* text for explanation of drugs and combinations.
†Total No. of patients.
‡6703 results are analyzed after 6 wks of induction therapy; for the other 3 studies late CRs are included.

using either daily oral CYT or methotrexate given orally twice weekly.

When we assessed the frequency of CRs obtained by Day 42, the VPS combination was found to be superior to the VP combination, but not significantly different from the other regimen (table 4).

The duration of remission was significantly longer with CYT maintenance than with methotrexate maintenance (4); in fact, the latter did not differ from that of a placebo control seen in a previous study (3). Survival was not different in the study regimens.

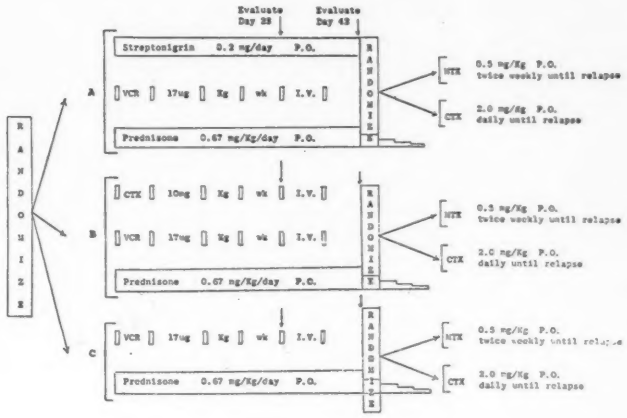
Evaluate Day 28
Evaluate Day 42
RANDOMIZE
A
Streptonigrin 0.2 mg/day P.O.
VCR 17ug Kg wk I.V.
Prednisone 0.67 mg/Kg/day P.O.
B
CTX 10mg Kg wk I.V.
VCR 17ug Kg wk I.V.
Prednisone 0.67 mg/Kg/day P.O.
C
VCR 17ug Kg wk I.V.
Prednisone 0.67 mg/Kg/day P.O.
RANDOMIZE
MTX
0.5 mg/Kg P.O. twice weekly until relapse
CTX
2.0 mg/Kg P.O. daily until relapse
If progressive disease at day 28 or no response or progressive disease at day 42, patient goes off study.

FIGURE 4.—Study design of ALB 6703.

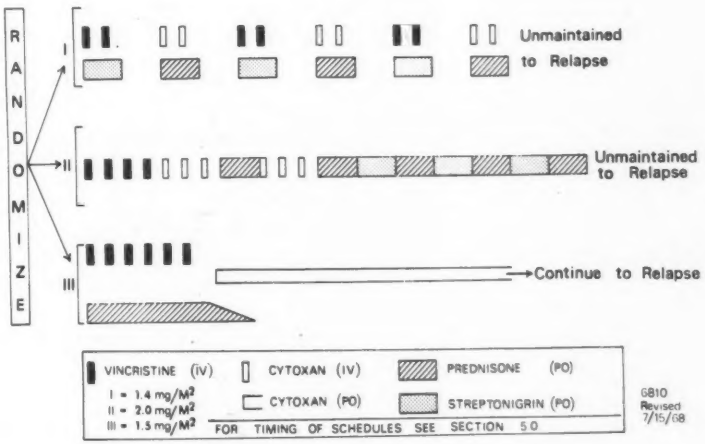

FIGURE 5.—Study design of ALB 6810.

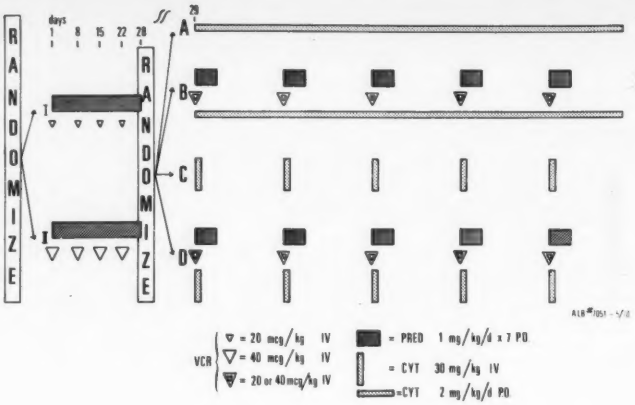

FIGURE 6.—Study design of ALB 7051.

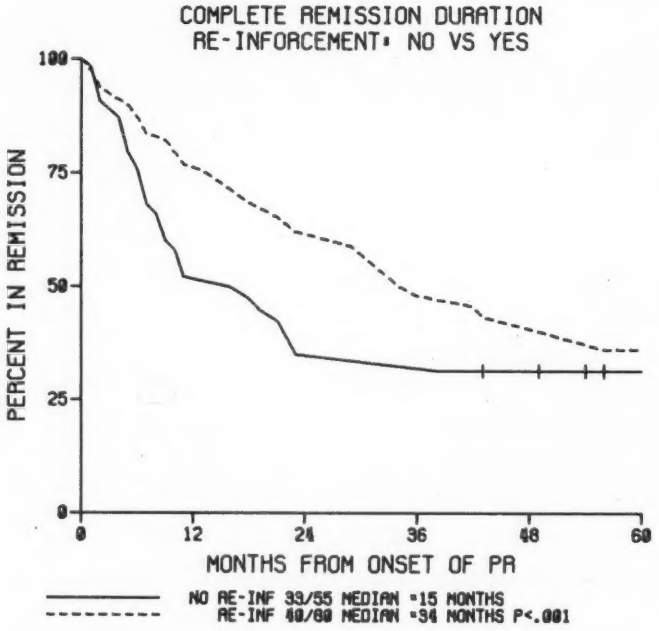

FIGURE 7.—Influence of reinforcement program in ALB 7051 on duration of CR.

TABLE 5.—Duration of CR in 3 CALGB studies according to study regimen and histology*

Study	Drugs†	Lymphocytic lymphoma		Reticulum cell sarcoma		Rappaport favorable		Rappaport unfavorable	
		No. of patients	Median duration of CR (mos)	No. of patients	Median duration of CR (mos)	No. of patients	Median duration of CR (mos)	No. of patients	Median duration of CR (mos)
6810	Combination VCR + SN + CYT + PRED	20	12.0	17	6.3	10	8.0	14	6.3
	Sequential VCR + SN + CYT + PRED	21	8.0	16	8.0	10	13.0	12	5.0
	VP → CYT	25	25.0	18	14.0	8	7.5	10	12.0
7051	Low VCR	49	21.1	23	22.6	17	15.5	30	21.9
	High VCR	40	50.1	37	19.3	19	>24	31	40.5
	No reinforcement	34	17.4	21	10.1	13	>24	25	10.0
	Reinforcement	48	32.0	31	38.9	20	16.2	30	>36
7253	VP	25	>22.0	19	19.4	—	—	31	25.3
	VPB	26	21.7	15	35.1	—	—	32	22.4
	VPS	14	>17.0	20	11.4	—	—	29	16.8
	VPBS	27	>24.0	27	12.5	—	—	37	>17.0

*6703 not included in this analysis due to small sample sizes.
†*See* text for explanation of drugs and combinations.

The simple VP combination was not inferior to the VPC regimen; it was therefore tested again in the next protocol, ALB 6810, which was chaired by D. Hayes and initiated in 1968. VP was given for 6 weeks and then followed by daily oral CYT maintenance therapy until relapse. This regimen was compared to a more intensive regimen of four drugs (VCR + SN + CYT + PRED) given either concurrently or sequentially at the same total dose over a 6-month period. The patients then were followed without maintenance therapy until relapse (fig 5).

The three programs gave essentially the same remission frequency (table 4), but, as shown in table 5, the duration of remission was considerably longer with the CYT maintenance than in the two programs unmaintained after 6 months (5).

For the subgroup reticulum cell sarcoma, the regimen of VP followed by CYT maintenance also prolonged survival as compared to the other two induction programs, while no difference can be seen yet in the other histologic subgroups.

The relatively simple regimen of VP induction followed by CYT maintenance thus appeared to be as good as or better than the more complex programs and it was examined in further detail in the subsequent study, ALB 7051, initiated in 1970, chaired by J. Moon and, after his death, by M. Flaherty.

In the induction phase the question of high versus low VCR dose in the VP combination was examined, and after 4 weeks of therapy the responders were randomized to daily oral CYT maintenance or high-dose iv CYT every 4 weeks. Furthermore, in each of these groups half of the patients received "reinforcement" treatment every 4 weeks consisting of 1 week of VP either in high or low dose as called for during induction (fig 6).

The results from the VCR dose comparison showed no overall difference with respect to remission frequency (table 4), but remission duration was prolonged by high VCR dose in three of four histologic subgroups (table 5). The VCR dose had no apparent influence on survival.

In the second phase of the study, the reinforcement program was highly successful (table 5 and fig 7); it led to a longer median duration of remission than CYT alone and, even more significant, to an improvement in survival (fig 8).

The question of whether daily oral or intermittent iv CYT is to be preferred in the maintenance program cannot yet be answered. For the two subgroups, lymphocytic lymphoma and favorable histologies, oral CYT seems to provide a longer duration of remission and survival than iv CYT. For the reticulum cell sarcomas, and for the unfavorable histologies, no difference can yet be seen.

The most recent study, ALB 7253, chaired by H. Blom, initiated in 1972, and closed in 1976, incorporated as a maintenance treatment daily oral CYT plus monthly reinforcements of VP, the principle which was identified as optimal in the previous protocol.

Improvement of results was sought in the induction phase by introducing SN in an intermittent weekly dose schedule in a combination with VCR + PRED (VPS), or by using bleomycin (BLEO) in

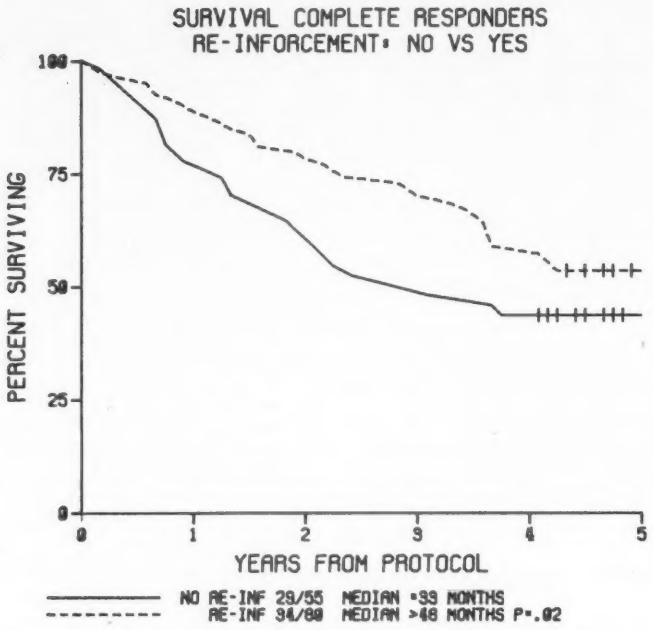

FIGURE 8.—Influence of reinforcement program in ALB 7051 on survival of patients who obtained CR.

combination with VCR + PRED (VPB), or by using all four drugs in the combination VCR + PRED + BLEO + SN (VPBS) and comparing them to VP alone (fig 9). Following the 6-week program, the responders were randomized between maintenance (as described above) and a consolidation program consisting of intermittent CCNU-vinblastine (VBL) + PRED for 4 months and then followed by the same maintenance program as the other group (fig 10).

The results from this protocol are not final because patients were entered until a few months ago. The preliminary analysis points toward an increased frequency of CRs with the two SN-containing programs in the reticulum cell sarcoma subgroup, and an increased frequency of response with the four-drug program in the DLWD subgroup (table 4). No advantage was seen from the CCNU + VLB + PRED consolidation phase.

The present study of stage III–IV non-Hodgkin's lymphoma in CALGB, activated only a few months ago, contains a multi-modality program. After an initial chemotherapy phase, it compares remission consolidation with intensive drug therapy, including adriamycin, with radiotherapy towards major sites of involvement; both programs are then followed by further maintenance therapy.

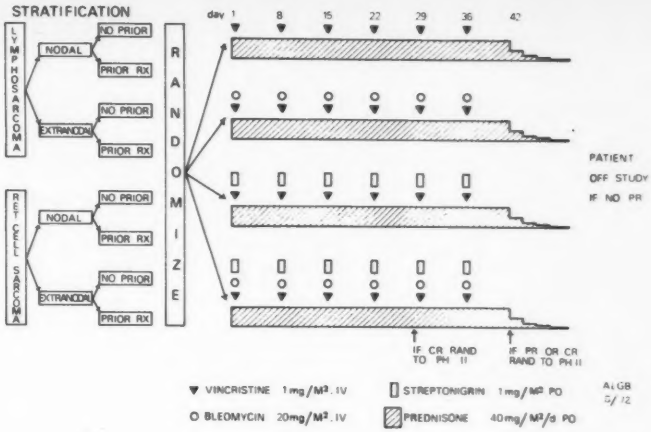

FIGURE 9.—Study design of induction phase of ALB 7253.

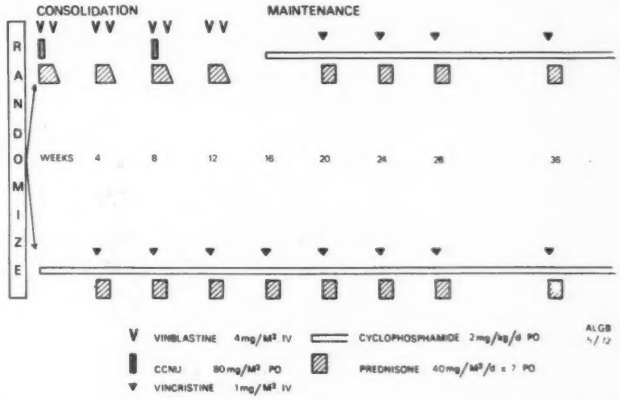

FIGURE 10.—Study design of maintenance phase of ALB 7253.

LIST OF COMPOUNDS

Bleomycin: NSC-125066; CAS reg. No. 11056-06-07; [2,4'-bithiazole]-4-carboxylic acid, 2'-(2-aminoethyl)-, monohydrate

CCNU: NSC-79037; CAS reg. No. 13010-47-4; urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate

Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-

Prednisone: NSC-10023; CAS reg. No. 53-03-2; pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-

Streptonigrin: NSC-45383; CAS reg. No. 632-62-2

Vinblastine: NSC-49842; CAS reg. No. 6649-03-2; vincaleukoblastine, sulfate (1:1), monohydrate

Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1)

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Combination Therapy for Diffuse Histiocytic Lymphoma That Includes Antimetabolites[1]

E. Cadman,[2,*] L. Farber,[2] D. Berd,[3] and J. Bertino[2,4]

SUMMARY

Thirty patients with diffuse histiocytic lymphoma (DHL) were treated with one of three regimens that included cyclophosphamide, vincristine, methotrexate with citrovorum factor rescue, and cytosine arabinoside. Twelve patients had a complete response with a predicted 50% survival of at least 76 months. The median survival of the 11 partial responders and seven nonresponders was 18 and 6 months, respectively. The addition of methotrexate and cytosine arabinoside may have a beneficial effect in therapy for DHL. From analysis of these results, there is reason to believe that efficacy may be partially dependent on the scheduling and dose of these two drugs.

[Cancer Treat Rep 61:1109–1116, 1977]

Diffuse histiocytic lymphoma (DHL) is the subclass of non-Hodgkin's lymphoma which responds least favorably to chemotherapy and has the worst prognosis (table 1) (1–14). Since 1969, the combination of cyclophosphamide, vincristine, methotrexate (MTX) with citrovorum factor rescue, and cytosine arabinoside (ara-C) (COMA) has been in use at Yale for the treatment of advanced DHL.[5] Thirty patients have received COMA therapy and have been evaluated.

METHODS

All patients with the diagnosis of DHL, stage III or IV, who were referred to Yale between March 1969 and June 1975 have received the COMA treatment program. No patient was refused treatment because of his clinical status. There were no patients withdrawn from the study or lost to followup. Staging laparotomies were not done routinely. Bone marrow aspirate and biopsy, liver-spleen scan, lymphangiogram, chest roentgenograms, hemogram, and serum chemistries constituted the staging procedure. Complete response (CR) was defined as no clinical or laboratory evidence of lymphoma for at least 2 months. A repeat biopsy of previous sites of tumor was not performed. A decrease in tumor size of $> 50\%$ was defined as a partial response (PR). Dr. R. Dorfman of Stanford (12) carried out the histologic verification of those patients who had entered the study from 1969 to 1971. Dr. J. Cornog of Yale evaluated the histology of patients treated after 1971.

Since its inception, the COMA program has been revised three times. The DHL No. 1 program was used from March 1969 to May 1971, the DHL No. 2 from May 1971 to January 1973, and the DHL No. 3 from January 1973 to June 1975 (table 2). The

[1] Supported in part by Public Health Service grants CA-08010 and CA-19892 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

[2] Departments of Medicine (E. Cadman, L. Farber, and J. Bertino) and Pharmacology (J. Bertino and E. Cadman), Yale University School of Medicine, New Haven, Conn.

[3] Fox Chase Cancer Center, Philadelphia, Pa.

[4] We thank Drs. S. Bobrow, W. B. Lundberg, D. Fisher, and A. Levy and the physicians of the Medical Oncology Section at Yale University School of Medicine for contributing patients to this study.

[5] Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate.

Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1).

Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-.

Citrovorum factor: NSC-3590; CAS reg. No. 6055-86-5; glutamic acid, *N*-[*p*-[[(2-amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxy-6-pteridinyl)methyl]amino]benzoyl]-, calcium salt.

Cytosine arabinoside: NSC-63878; CAS reg. No. 69-74-9; cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride.

*Reprint requests to: E. Cadman, MD, Yale University School of Medicine, 333 Cedar St, New Haven, Conn 06510.

TABLE 1.—DHL therapy

Ref No.	No. of patients	Complete response		Partial response		No. of relapses (%)	Median survival (mos) for—		Drug regimen*
		No.	%	No.	%		CR	Other	
1	19	1	5	13	69	—	5	—	Cyclophosphamide
2	19	2	10	14	70	—	—	—	Adriamycin
3	13	2	15	5	38	—	—	—	CVP
4	6	1	16	2	33	—	3	—	VP
4	4	1	25	1	25	—	11+	—	COPP
5	78	20	26	21	27	—	20	6	CVP ± bleomycin ± mechlorethamine
2	34	13	38	—	—	—	—	—	CVP
2	32	14	43	—	—	—	—	—	Adriamycin-prednisone + bleomycin
6	27	11	41	8	29	1	41+	5	MOPP/COPP
7	28	14	50	7	25	—	24	8.5	CVP + BCNU
8	15	9	60	—	—	—	—	—	CVP + bleomycin
9	35	23	65	9	25	6(17)	12+	—	CHOP + bleomycin
10,11	—	—	70	—	—	(22)	—	—	HOP/CHOP
12	8	6	75	1	13	1(13)	65+	—	COMA
13	9	9	100	—	—	2(23)	2–20	—	COMA
14	10	10	100	—	—	5(50)	13	—	COM

*CVP = cyclophosphamide, vincristine, and prednisone; VP = vincristine and prednisone; COPP = cyclophosphamide, vincristine, prednisone, and procarbazine; MOPP = mechlorethamine, vincristine, prednisone, and procarbazine; CHOP = cyclophosphamide, adriamycin, vincristine, and prednisone; HOP = adriamycin, vincristine, and prednisone; and COM = cyclophosphamide, vincristine, and MTX.

TABLE 2.—DHL treatment schedules

Regimen*	Dose	Day of treatment												
		0	1	8	15	22	29	36	43	50	57	64	71	78	85
Protocol 1															
Cyclophosphamide	1.5 mg/m² iv	×													
Vincristine	1.4 mg/m² iv		×	×	×										
MTX	30 mg/m² q6h × 4 oral					×	×	×	×	×	×	×	×		
Citrovorum factor	25 mg q6h × 4 oral 24 hrs after MTX					×	×	×	×	×	×	×	×		
Ara-C	300 mg/m² iv 16 hrs after MTX					×	×	×	×	×	×	×	×		

*Revisions:		Schedule for protocol—	
	Drug	2	3
	MTX	80 mg/m² iv	120 mg/m² iv
	Citrovorum factor	25 mg q8h × 3 oral	25 mg q6h × 4 oral
	Ara-C	300 mg/m² with MTX	300 mg/m² with MTX
	Prednisone	100 mg/m² qd × 5 oral	—
	Wks of MTX × ara-C	3	8

duration of chemotherapy was a maximum of 9 months. Protocols 1 and 3 were similar in drug dosages (*see* table 2). Each cycle of these two protocols consists of cyclophosphamide on Day 0 and vincristine on Days 1, 8, and 15 with MTX, ara-C, and citrovorum factor administered for the next 8 consecutive weeks. The cycle was repeated three times. Because these two protocols were similar in drug doses and frequency of drug administration, the results were combined in calculating the life-table analysis (fig 1).

RESULTS

Tables 3–5 present summaries of patient characteristics, prior therapy, and response to COMA. There were 12 women and 18 men. Eleven patients were stage IV-B, 13 patients were stage IV-A, two patients were stage I-A, and one each was stage II-EA, I-EA, I-B, and II-A. Except for three patients, the lower stages had all relapsed to stage IV status following radiotherapy and before the beginning of COMA. Patient 14 (I-B), in spite of no evidence of

TABLE 3.—DHL protocol 1

Patient No.	Sex	Age (yrs)	Stage	Disease sites	Previous treatment	Relapse	Response	After DHL protocol: Mos disease free	After DHL protocol: Mos alive	Status	Comment*
1	F	48	IV-B	Abdominal mass, colon	Colostomy; 3000 rads to abdomen	Chest (1 mo)	PR	0	7	Dead	PR with C-V relapse after 2nd M-A
2	M	61	IV-B	Skin	—	—	PR	0	18	Dead	PR while receiving M-A
3	M	64	IV-A	Epidural, retroperitoneal	Laminectomy; 3600 rads	Spleen/liver (2 mos)	CR	6	13	Dead	Recurrence after 2nd cycle with M-A
4	M	58	IV-B	Retroperitoneal, positive lymphangiogram	3400 rads	—	CR†	72+	72+	Alive	—
5	M	16	IV-A	Lung mass hilum, neck, positive bone marrow biopsy	—	—	CR	79+	79+	Alive	CR after 1st C-V
6	M	65	IV-A	Parotid	3500 rads	Nodes (4 mos)	CR	56+	64+	Alive	CR after completion of 1st cycle
7	M	41	IV-B	Skin, pleural effusion	—	—	CR	2	10	Dead	Recurrence during M-A of 2nd cycle
8	F	32	IV-A	Pelvic mass, ovaries, bowel	Laparotomy; 1625 rads whole abdomen	Nodes, pleural effusion, bone (3 mos)	CR	72+	72+	Alive	CR after 1st C-V
9	F	52	IV-A	Right eyelid	4000 rads to right eye	Bile duct obstruction (3 mos)	CR	56	75	Dead	Relapse treated with DHL protocol 3; had marked response after C-V, but recurred during M-A
10	M	68	IV-A	Epigastric mass, pleural effusion, nodes	—	—	None	0	1	Dead	Died of gastrointestinal bleeding before M-A given
11	F	56	IV-A	Nodes, breast, mediastinum, pleural effusion	5-FU and 1600 rads	—	CR	2	13	Dead	CR after 1st cycle, recurrence during M-A of 2nd cycle; response after 3rd C-V, but return during M-A

*C-V = cyclophosphamide-vincristine; M-A = MTX-ara-C.
†Lymphangiogram negative at 3½ years.

TABLE 4.—DHL protocol 2

Patient No.	Sex	Age (yrs)	Stage	Disease sites	Previous treatment	Relapse	Response	After DHL protocol: Mos disease free	After DHL protocol: Mos alive	Status	Comment*
12	M	65	IV-A	Nodes, retroperitoneal, bone	4000 rads inverted Y	Nodes (4 mos)	PR	0	16	Dead	Response occurred in 1st week following C-V, recurrence during M-A
13	F	15	I-EA	Clavicle	5400 rads	Neck mass, flank mass (36 mos)	None	0	9	Dead	Given 2½ cycles
14	M	43	I-B	Right axillary node; laparotomy negative	—	—	CR	48+	48+	Alive	Local radiotherapy begun at same time as DHL protocol
15	M	24	IV-B	Nodes, lung, cardiac tamponade	—	—	PR	0	27	Dead	Lung mass and pericardial effusion gone after 1st C-V, cord compression after 5 mos of treatment
16	F	25	II-EA	Mediastinum, lung	500 rads to mediastinum	—	PR	0	10	Dead	90% regression after C-V, recurrence during M-A of 4th cycle
17	M	42	IV-B	—	—	—	PR	0	6	Dead	Response after C-V, recurring after M-A
18	F	57	IV-A	Retroperitoneal mesentery	—	—	PR	0	9	Dead	Left eye DHL 2 wks after 3rd cycle

*C-V = cyclophosphamide-vincristine; M-A = MTX-ara-C.

TABLE 5.—DHL protocol 3

TABLE 5.—DHL protocol 3

Patient No.	Sex	Age (yrs)	Stage	Disease sites	Previous treatment	Relapse	Response	After DHL protocol: Mos disease free	After DHL protocol: Mos alive	Status	Comment*
19	M	73	II-A	Neck nodes	3500 rads	Nodes (7 mos)	PR	0	19	Dead	90% regression 2 wks after C-V, nodes increased during M-A of 3rd cycle; regression again following cyclophosphamide
20	M	80	IV-B	Liver, kidney, duodenum	3000 rads	—	None	0	2	Dead	—
21	F	84	IV-B	Scalp/nodes, liver, spleen	—	—	PR	0	24	Dead	80% regression after C-V, increased with M-A; stopped after first cycle
22	M	82	IV-B	Retroperitoneal, liver	—	—	PR	0	29+	Alive	Regression after C-V, increased after M-A; protocol stopped after ½ cycle
23	M	42	IV-B	Bowel, nodes, lungs	—	—	None	0	6	Dead	Disease progressed with M-A
24	F	62	IV-B	Stomach, spleen, nodes	—	—	None	0	2	Dead	Died of gastrointestinal bleeding
25	F	25	IV-A	Retroperitoneal, scalp	3000 rads	Scalp (9 mos)	PR	0	17+	Alive	Decrease after C-V, increase after M-A, off protocol after 2nd cycle
26	F	72	I-A	Neck nodes	4000 rads	Breast, skin, nodes (12 mos)	CR	21+	21+	Alive	—
27	M	51	IV-A	Stomach, nodes	3600 rads	Nodes (12 mos)	CR	6	9+	Alive	Relapse at end of 3rd cycle, abdominal mass
28	F	25	IV-A	Bowel, nodes	—	—	None	0	8+	Alive	Progression on M-A of 1st cycle; off protocol
29	M	43	I-A	Mediastinum	4000 rads	—	None	—	19	Dead	Progression after 1st M-A (tonsil, nodes, and hoarseness), lung after 2nd M-A cycle, > 50% decrease after C-A
30	M	28	IV-A	Stomach, spleen, bowel	—	—	CR	10	12	Dead	Relapse 2 mos after last cycle

*C-V = cyclophosphamide-vincristine; M-A = MTX-ara-C; C-A = cyclophosphamide-adriamycin.

TABLE 6.—Median survival*

Response	Duration (mos)
None	6
PR	18
CR	48+
Relapse after CR	9

*Complete responders are alive at 9, 21, 48, 64, 72, 72, and 79 mos; 1 died at 75 mos.

lymphoma at laparotomy, was given COMA because the B symptoms were thought to be a manifestation of disseminated disease. He is currently in an unmaintained CR at 48 months. Patient 16 (II-EA), who had a mediastinal mass and contiguous pulmonary parenchymal involvement, died 10 months following a PR. Patient 29 (I-A), who had only a mediastinal mass, was given COMA as an adjunct after radiation of 4000 rads to a mantle port. He developed new disease within the irradiated field during the first cycle of drugs and died 19 months after the beginning of chemotherapy.

The median survival from the onset of chemotherapy depended upon whether a remission was achieved (table 6). Those patients who did not respond had a median survival of 6 months. Patients who had a PR lived a median of 18 months. The median survival has not yet been reached in those patients who had a CR; currently, it is > 48 months. Life-table analysis of protocols 1 and 3, which are almost identical, predicts that the 50% probability of survival will be 76 months (fig 1). This is significantly different from the survival curves of the partial responders or nonresponders ($P < 0.01$).

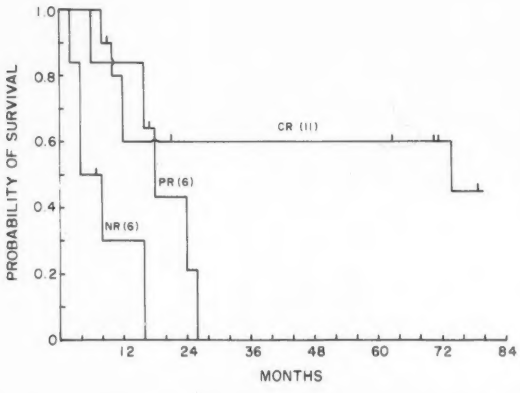

FIGURE 1.—Survival of patients in DHL protocols 1 and 3.

Six of the 12 patients who had a CR have relapsed. Their median survival from relapse was 9 months. All relapses occurred within 12 months except in patient 9 who relapsed at 56 months and died 19 months later.

Eight of the 12 patients who achieved a CR were treated with DHL protocol 1. Four of these eight patients have relapsed at 2, 2, 6, and 56 months. DHL protocols 2 and 3 produced one and three CRs, respectively (table 7). Ten of the 12 CRs occurred after the initial cyclophosphamide-vincristine injection and before the MTX-ara-C therapy began. The two exceptions were treated with the DHL protocol 1. Both patients were in CR after the first cycle of therapy. Patient 6 continues in CR at 64 months; patient 11 relapsed during the MTX-ara-C portion of the second cycle.

Of the six patients with a CR who relapsed, four were treated with the DHL No. 1 program. Three of the four relapsed while receiving the MTX-ara-C portion of their therapy. The fourth patient, No. 9, was treated a second time with DHL No. 3 and this resulted in a dramatic tumor response following cyclophosphamide-vincristine; however, the lymphoma returned during the subsequent MTX-ara-C therapy. The remaining two relapses in patients with CR (Nos. 27 and 30) occurred in protocol 3; both patients relapsed shortly after completion of the chemotherapy program. Relapses of disease in all six patients were at sites of previous involvement, suggesting that disease persisted in these areas.

Ten of the 11 PRs occurred during the initial cyclophosphamide-vincristine therapy and one (patient 2) during the initial MTX-ara-C therapy in DHL protocol 1 (table 8).

Generally, the drugs were well tolerated. Two of four patients with gastrointestinal lymphoma died from gastrointestinal bleeding within the first week following the initial cyclophosphamide and vincristine (patient 10, protocol 1, and patient 24, protocol 3). These elderly patients, who had stomach involvement, presumably died as a result of tumor necrosis and drug-induced thrombocytopenia.

TABLE 7.—Summary of the 3 DHL treatment programs

	DHL protocol—			Total (%)
	1	2	3	
No. of patients	11	7	12	30
No. of PRs	2	5	4	11(36)
No. of CRs	8	1	3	12(40)
No. of relapses after CR	4	0	2	6(50)

TABLE 8.—Occurrence of response and relapse

Part of cycle	Occurrence in—			
	Complete responders		Partial responders	
	Response	Relapse	Response	Relapse
Cyclophosphamide-vincristine	10		10	
MTX-ara-C	2	3	1	11
After therapy was completed		3		

TABLE 9.—Chemotherapy of DHL with regimens that include antimetabolites

Program	No. of patients	CR (%)	PR (%)	Median survival (mos)	
				CR	Other responders
COMA					
Yale	30	40	36	48+	12
University of Chicago	22	68	27	12+	—
CAT					
Stanford	18	44	33	5+	—
MEV*					
University of Bologna	10	100	—	13	—

*MEV = methotrexate, cyclophosphamide, and vincristine.

DISCUSSION

The COMA program was formulated to treat reticulum cell sarcoma on the basis of certain characteristics of this aggressive lymphoma and for theoretic reasons (table 9). It was reasoned that the antimetabolites MTX and ara-C, which have transient effects on this disease, would be more effective if used when the tumor cell burden was markedly decreased and when the cells would be in log-phase growth. Since cyclophosphamide and vincristine are effective antilymphoma agents, even in the presence of bulky disease, we initiated treatment with these agents. MTX and ara-C were used in combination beginning 3 weeks after cyclophosphamide and vincristine. This decision was based upon studies of L5178Y cells in vitro (15), and experimental studies of L1210 leukemia indicating that concomitant treatment with MTX or a 10-hour interval between MTX and ara-C administration increased the antitumor effects of ara-C (16). A 24-hour exposure to MTX was obtained by administering the dose every 6 hours × 4 to encompass at least one generation time of this rapidly growing tumor. Eight weekly doses of MTX-ara-C were then administered to obtain additional cell kill. Three such cycles were administered, based upon the observation that the therapy, if successful, should result in disappearance of all clinical disease by the end of the first cycle; cycles 2 and 3 were added to ensure eradication of foci of microscopic disease ($\leq 10^{x}$ cells). Before the review of the first 17 patients treated according to the newly accepted Rappaport classification was completed (12), we concluded that decreasing the number of weeks of MTX-ara-C to three would be of benefit and would allow us to administer more cycles with a greater total dose of cyclophosphamide and vincristine. In addition, prednisone[6] was added to the treatment regimen. When a review of the original 17 patients revealed that only 11 had DHL, and that eight of the nine patients with CR were in this group, we abandoned protocol 2 because preliminary results from it were not as good as those from protocol 1. Protocol 3 was then initiated; essentially it is the same as the original protocol, except that the MTX is administered as a single iv dose just before the ara-C. The results of this last protocol have not been as good as those of protocol 1 although it is difficult to compare the data with confidence because of the small numbers of patients involved and the older age of the patients in protocol 3—five of 12 patients were > 70 years old. In all three programs it is clear that most relapses occur during the MTX-ara-C part of the cycle. Since 75% of the cycle is

[6] Prednisone: NSC-10023; CAS reg. No. 53-03-2; pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-.

occupied with administration of these drugs, this may have occurred by chance, and the patients may have been destined to relapse anyway. Alternately, it may be that this part of the combination is ineffective, or effective only in circumstances where the cyclophosphamide-vincristine have achieved complete tumor regression, thus leaving only microscopic disease for eradication by the antimetabolite combination. It is clear that the dose and schedule of the antimetabolites may not be optimum, and perhaps patients may require larger weekly doses of MTX which will ensure higher blood levels for at least 24 hours. This increase in dose may be accomplished with safety, especially with current regimens employing alkalinization of urine with bicarbonate (17). It remains to be determined whether the striking results seen with protocol 1 were the result of patient selection or were due to the drug scheduling (MTX given every 6 hours × 4). Sweet et al (13), who have also used COMA according to protocol 3 (with dose escalations of MTX), have reported a 100% CR rate, with a followup ranging from 2 to 20 months. Another study recently reported excellent results using MTX as part of a combination to treat DHL. Lauria's program included cyclophosphamide (800 mg/m² iv on Day 1), MTX (20 mg/m² im on Day 3), and vincristine (2 mg/m² iv on Day 4). Each cycle was repeated at 12–15 days. All ten patients with DHL treated achieved a CR; of these, five have relapsed at 2, 2, 8, 8, and 17 months (14).

The CAT (ara-C, adriamycin, and 6-thioguanine) program of Rosenberg[7] includes antimetabolites and is essentially the same as that used to treat acute myelogenous leukemia (table 9). In this program, ara-C and 6-thioguanine are administered daily for 14 days, beginning the day after adriamycin. A CR rate of 44% (eight of 18) has been reported, but most patients have relapsed within a few months.

These and other studies (6,7) indicate that if a CR is attained the patients have a good chance of cure. Six of our 12 complete responders are long-term survivors; they are free of disease at 21, 48, 64, 72, 72, and 79 months. One patient relapsed after being in CR for 56 months (he was the only patient who relapsed after a 12-month disease-free interval). The rapid appearance of disease at 2, 2, 6, 6, and 10 months in the other five who achieved a "CR" suggests that these patients may not actually have had a CR. Careful restaging and perhaps additional chemotherapy or radiotherapy to areas of known disease as in the treatment of Hodgkin's disease (18) may reduce the frequency of these relapses.

[7] Rosenberg S. Personal communication.

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Non-Cross-Resistant Combinations in Stage IV Non-Hodgkin's Lymphomas [1]

Gianni Bonadonna,* Silvio Monfardini, and Eugenio Villa [2]

SUMMARY

Two triple-drug combinations (cyclophosphamide, vincristine, and prednisone [CVP] and adriamycin, bleomycin, and prednisone [ABP]) were randomly tested in 57 consecutive patients with pathologic stage IV non-Hodgkin's lymphoma. No statistical difference was observed in the incidence of complete remission (CR) (48% vs 50%), median duration of CR (10.5 vs 20.5 months), and survival. CR correlated positively with survival. After crossover for progression or relapse, no cross resistance was detected between the two combinations (CR plus PR = 40% for CVP and 50% for ABP). In a subsequent prospective study CVP and ABP were sequentially alternated in an attempt to improve the incidence and duration of CR. In the first 32 evaluable patients CR was produced in 50%. The findings are still preliminary.

[Cancer Treat Rep 61:1117–1123, 1977]

Recent experience in advanced stage III and IV non-Hodgkin's lymphoma suggests that multiple-drug regimens increase the incidence of complete remission (CR) and prolonged survival compared to single-agent chemotherapy (1). However, even if a small fraction of patients with diffuse histiocytic lymphoma can achieve cure after cyclic chemotherapy (2), the treatment of choice for this complex group of diseases has not yet been identified. On the contrary, the data reported in the literature (1) show that little advantage is obtained by simultaneously adding a fourth or fifth agent to an effective triple-drug regimen. It seems probable that even with the optimal use of the available compounds we are approaching a plateau in the control of disseminated non-Hodgkin's lymphomas.

It is well known that, despite a high incidence of prompt tumor shrinkage, early relapses are frequent and an effective second-choice regimen has not been defined for patients with either relapse or progressive disease. In the past 3 years we have explored the possibility of developing non-cross-resistant combinations, and we have reported previously the initial findings of a controlled pilot study (3,4). The purpose of this paper is to summarize the results obtained with two non-cross-resistant regimens: cyclophosphamide, vincristine, and prednisone (CVP) and adriamycin, bleomycin, and prednisone (ABP).[3]

Patients and Methods

The purpose of the study was to compare in patients with biopsy-proved stage IV disease the efficacy (incidence of CR) of CVP versus ABP, and to demonstrate the absence of cross resistance between the two combinations. Patients were classified histologically according to the criteria of Rappaport and staged by the Ann Arbor system. Besides conventional radiologic examinations (roentgenogram of chest, skeleton, and gastrointes-

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[3] Cyclophosphamide: NSC-26271; CAS reg. No. 6055–19–2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate.

Vincristine: NSC-67574; CAS reg. No. 2068–78–2; leurocristine, sulfate (1:1).

Prednisone: NSC-10023; CAS reg. No. 53–03–2; pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-.

Adriamycin: NSC-123127; CAS reg. No. 23214–92–8.

Bleomycin: NSC-125066; CAS reg. No. 11056–06–7; [2,4'-bithiazole]-4-carboxylic acid, 2'-(2-aminoethyl)-, monohydrate.

TABLE 1.—Dose-reduction schedule

Leukocytes/mm³	Platelets/mm³	Next dose*
≥4000	≥130,000	100% of all drugs
3999–3000	130,000–80,000	50% CYT, ADM
2999–2000	80,000–50,000	50% VCR; 25% CYT, ADM
1999–1500		25% VCR; no CYT, ADM
<1500		Only PRED, BLEO

*CYT = cyclophosphamide; ADM = adriamycin; VCR = vincristine; PRED = prednisone; BLEO = bleomycin.

tinal tract, and bipedal lymphography), all patients had unilateral bone marrow biopsy with the Jamshidi needle. Liver biopsies were carried out during laparoscopy and/or laparotomy.

Figure 1 presents an outline of the study. CVP was administered according to the dose schedule designed at the NCI, Bethesda, Md (5). Cyclophosphamide and prednisone were given orally from Day 1 to 5 at doses of 400 and 100 mg/m² respectively; vincristine was injected iv on Day 1 of each cycle at a dose of 1.4 mg/m². ABP included adriamycin administered iv on Day 1 (75 mg/m²), bleomycin on Days 1 and 8 (15 mg/m²), and prednisone at the same dose as in CVP. Both CVP and ABP were repeated every 3 weeks. Table 1 shows the dose-reduction schedule adopted in the presence of myelosuppression. Patients started on ABP were also crossed over to CVP after total doses of 550–600 mg/m² of adriamycin and 200–250 mg/m² of bleomycin. The third-line treatment included CCNU, 100 mg/m² orally every 6 weeks.[4]

Table 2 presents the main characteristics of the evaluable patients. All patients receiving a minimum of three cycles of either combination or with signs of progressive disease after at least two cycles were considered evaluable for therapeutic response. Of 62 consecutive patients admitted to the study from October 1972 to October 1974, five were not considered evaluable (two receiving CVP and three receiving ABP) either because of irreversible marrow aplasia after one or two cycles of treatment (3) or because of inadequate re-evaluation of initial tumor parameters (2). Previous drug therapy consisted of an incomplete course with single- or multiple-agent chemotherapy.

A patient was considered in a state of CR when all symptoms and signs of disease had disappeared and all roentgenographic, radioisotopic, and biochemical changes had returned to normal. Furthermore, a second biopsy of accessible extralymphatic sites of known involvement such as liver (laparoscopy) and bone marrow (needle biopsy) had to be interpreted as negative. Partial remission (PR) was defined as a ≥ 50% reduction in the sums of the products of the longest perpendicular diameters of all measurable evidence of disease. Patients with regression of < 50% (objective improvement) or no change in measured tumors by the end of the sixth cycle or with relapse (regrowth of tumor masses and/or appearance of new lesions) during the first six cycles were all considered induction failures.

[4]CCNU: NSC-79037; CAS reg. No. 13010-47-4; urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-.

TABLE 2.—CVP vs ABP: main characteristics of evaluable patients

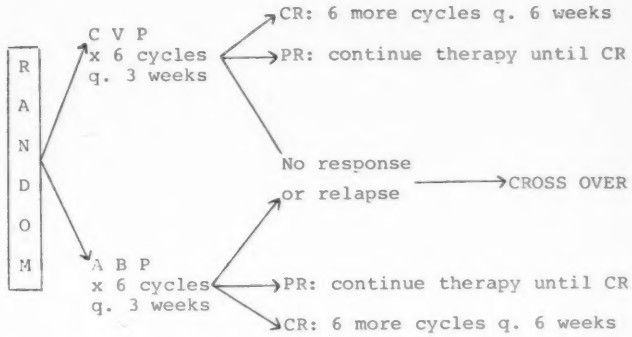
	CVP (27 patients)	ABP (30 patients)
Mean age in yrs (range)	52.0 (22–68)	52.5 (6–71)
Men	17	19
Women	10	11
Median time from diagnosis to treatment in mos (range)	2.0 (0–11)	2.5 (0–13)
Histologic type		
Lymphocytic	12	13
Histiocytic	14	15
Mixed type	1	2
Nodular pattern	5	5
Diffuse pattern	22	25
Prior therapy		
None	18	21
Radiotherapy	6	6
Chemotherapy	3	3

Primary and Secondary Response

Table 3 shows that we observed no statistical difference between the two treatment groups in the incidence of response or in the median duration of CR. Three of ten patients (CVP, one of four; ABP, two of six) with diffuse histiocytic lymphoma achieved sustained CR. At the time of this writing, they are free of disease for a minimum of 21+ to a maximum of 26+ months. Five of ten patients (CVP, two of five; ABP, three of five) with well-differentiated lymphocytic lymphoma (nodular and diffuse) have remained in CR for periods ranging from 15+ to 31+ months.

Table 4, which presents the results of crossover treatment, indicates that there is no cross resistance between CVP and ABP. Furthermore, four of ten patients treated with CCNU showed response (three CRs, one objective improvement).

As illustrated in figure 2, the difference between the survival of complete and of non-complete responders was significant (CVP, $P = 0.02$; ABP, $P =$



STRATIFICATION: 1. Stage: clinical or pathologic
2. Pattern: nodular or diffuse
3. Type: histiocytic, lymphocytic, mixed

FIGURE 1.—CVP vs ABP: outline of study.

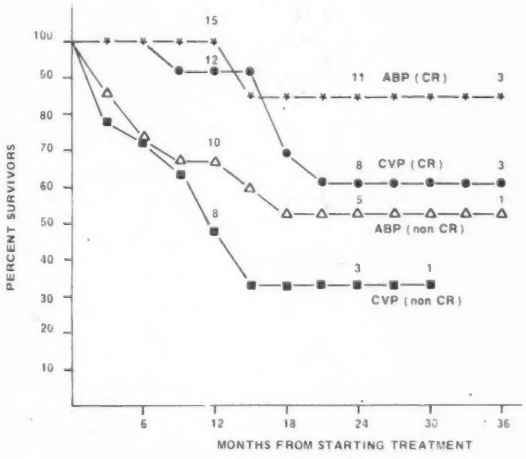


FIGURE 2.—CVP vs ABP: actuarial survival of patients achieving and not achieving CR.

0.03) in both treatment groups. In fact, 2 years after starting treatment, complete remitters had not reached the median. Also, at this time no significant difference was seen between the whole group treated with CVP and that treated with ABP.

Toxicity

A previous paper (4) described the side effects in considerable detail. Table 5 lists all toxic manifestations observed in the series, including those patients considered not evaluable for therapeutic purposes. As can be seen, the main dose-limiting factor in both treatment groups was myelosuppression and it was responsible for the death (via infection and/or hemorrhage) of six of 63 patients (three from each regimen). A seventh patient died of irreversible cardiomyopathy because the local physician erroneously administered adriamycin up to the total dose of 700 mg/m^2. The second patient, who developed cardiac toxicity after a total dose of 637 mg/m^2, recovered after intensive supportive therapy; he is well and free of disease 2½ years after his recovery from heart failure. In four patients repeated chest roentgenograms detected early signs of bleomycin-induced interstitial pneumonitis. This lung toxicity was asymptomatic and resolved with prompt discontinuance of the drug.

Table 6 records the percent of optimal dose that could be administered in each of the first six cycles during primary treatment. No significant difference was seen between the two combinations.

TABLE 3.—Comparative response to primary treatment

	Histology					
	Nodular	Diffuse	Lymphocytic	Histiocytic	Mixed	Total
			CVP			
Patients	5	22	12	14	1	27
CR + PR (%)	80	73	75	71	100	74
CR (%)	80	41	58	36	100	48
Median duration of CR (mos)	3	10	16	9	7	10.5
			ABP			
Patients	5	25	13	15	2	30
CR + PR (%)	100	72	77	80	50	77
CR (%)	80	44	62	40	50	50
Median duration of CR (mos)	6	23	9	23	21+	20.5
P value of CR duration	0.67	0.12	0.81	0.08		0.24

TABLE 4.—Response after crossover

	CVP	ABP
Total with response/total crossed over	6/15 (40%)	6/12 (50%)
CR	5	2
Median duration of CR + PR (mos)	11.5	17

TABLE 5.—CVP vs ABP: toxic manifestations after primary treatment

	CVP (30 patients)		ABP (33 patients)		Mean toxic dose in mg/m² (range)
	No.	%	No.	%	
Leukopenia*	19	63	15	45	
Thrombocytopenia	7	23	11	33	
Stomatitis	3	10	8	24	
Neurotoxicity	16	53			
Loss of hair	26	87	28	85	
Cystitis	2	7			
Gastritis	2	7	3	9	
Skin changes			12	36	
Bleomycin pneumonitis			4	12	142 (60–240)
Cardiomyopathy			2	6	668 (637–700)
Drug-related deaths	3	10	4	12	
Infection	2	7	2	6	
Hemorrhage			1	3	
Both	1	3.5			
Cardiotoxicity			1	3	

*Leukocytes $<4000/mm^3$.
†Platelets $<130,000/mm^3$.

TABLE 6.—Percent of optimal dose per cycle

	Cycles						Average total course
	1	2	3	4	5	6	
Cyclophosphamide	94	74	74	73	86	78	80
Vincristine	100	89	92	89	85	83	90
Prednisone	98	93	96	93	93	96	94
Adriamycin	89	79	80	85	77	82	82
Bleomycin	98	95	86	83	73	64	84
Prednisone	98	90	93	92	94	98	94

CVP PLUS ABP

Patients and Methods

This study was also designed to determine whether the incidence of CR and the duration of response in patients with biopsy-proved stage IV non-Hodgkin's lymphoma could be improved by alternating CVP with ABP. Histologic criteria, staging system, and parameters of drug response were identical to those described for the previous study.

CVP was administered according to the standard dose schedule (5). In the ABP regimen, adriamycin was reduced to 60 mg/m^2 and bleomycin to 10 mg/m^2. In the absence of relapse or progression, each combination was alternated every 3 weeks for a total of six cycles. In the presence of clinical CR at the end of the sixth cycle, six more alternating courses were given. At the end of the 12th cycle, the patients were restaged by laparoscopy and marrow biopsy; if CR was confirmed on histopathologic grounds, treatment was discontinued. If by the sixth cycle only a good PR was obtained, treatment was continued until clinical CR was documented. Then, six additional cycles were given every 6 weeks followed by restaging procedures. During sequential therapy we employed the same dose-reduction schedule (table 1). Patients who showed progression or relapse during the first 12 cycles were removed from the study and treated with CCNU (100 mg/m^2 every 6 weeks orally) plus vinblastine (6 mg/m^2 every 10 days iv).[5]

Between November 1974 and July 1976, 55 consecutive patients were admitted to this prospective study. At the time of this report, only 32 patients are considered evaluable, either because they have completed 12 cycles or because relapse was documented during sequential chemotherapy. Table 7 presents the main features of the evaluable patients. It is important to note that the clinical and histopathologic findings are similar to those of patients presented in table 2. In two patients it was impossible to classify the histologic type, while in four the extranodal specimen submitted to the pathologist was too small to permit the diagnosis of nodular or diffuse pattern. In this series also, prior chemotherapy consisted of an inadequate course with either single agents or combinations.

TABLE 7.—CVP alternated with ABP: main characteristics of evaluable patients

Patients	32
Mean age in yrs (range)	49.5 (23–62)
Men	18
Women	14
Median time from diagnosis to treatment (mos)	1.4
Histologic type	
Lymphocytic	11
Histiocytic	10
Mixed type	9
Unclassified	2
Nodular pattern	2
Diffuse pattern	24
Extranodal	4
Prior therapy	
None	25
Radiotherapy	3
Chemotherapy	4

Results

At the present time we have no evidence that sequential chemotherapy produced a higher incidence of CR than either CVP or ABP given alone (table 8). However, these findings should be considered as preliminary; a long-term analysis may reveal an improved duration of response after sequential treatment.

Toxicity

The incidence of some of the toxic signs, namely myelosuppression, neurotoxicity, and hair loss, was higher than reported after either CVP or ABP

[5]Vinblastine: NSC-49842; CAS reg. No. 6449-03-2; vincaleukoblastine, sulfate (1:1), monohydrate.

TABLE 8.—Response to sequential treatment

Histologic type	Patients	CR + PR (%)	CR (%)	Median duration from cessation of all therapy (mos)
Nodular	2	100	50	7
Diffuse	24	70	41	4+
Lymphocytic	11	81	36	2.5+
Histiocytic	10	60	50	6+
Mixed type	9	77	44	3+
Unclassified	2	100	100	2+
Total	32	75	50	4+

TABLE 9.—Sequential chemotherapy: toxic manifestations

	Patients	%
Leukopenia	25	78
Thrombocytopenia	23	71
Stomatitis	7	21
Neurotoxicity	21	65
Ileum	2	6
Loss of hair	32	100
Cystitis	4	12.5
Gastritis	5	15
Skin changes	10	31
Bleomycin pneumonitis	1	5

TABLE 10.—Percent of optimal dose per cycle after sequential chemotherapy

	Cycles												Average total course
	1	2	3	4	5	6	7	8	9	10	11	12	
Cyclophosphamide	98		93		81		77		77		76		84
Vincristine	100		98		90		95		90		92		94
Prednisone	96		91		94		86		77		76		87
Adriamycin		82		78		88		80		85		78	82
Bleomycin		100		99		97		92		89		86	94
Prednisone		91		90		95		85		79		90	83

given alone (table 9). However, no drug-related deaths were observed, and sequential treatment was compatible with a high total percent of optimal dose (table 10).

CONCLUSIONS

Our results indicate that in patients with stage IV non-Hodgkin's lymphomas the combinations CVP and ABP are equally effective and show no cross resistance. We need an effective second-line treatment because only about half of the patients with advanced disease achieve a pathologically documented CR with available combinations (1). From this point of view, CVP and ABP appear to be useful combinations considering that the patients responded to primary and secondary treatment irrespective of histologic pattern and type. It is also important to note that CCNU administered as a third-line treatment produced some CRs.

Since it is theoretically possible to increase both incidence and duration of CR by the appropriate alternation of two non-cross-resistant combinations, CVP and ABP were administered in a sequential fashion. Because of the limited number of patients presently evaluable, no firm conclusions can yet be drawn. However, preliminary findings seem to indicate that sequential treatment did not increase the percent of CR; we have not yet fully evaluated the impact of such treatment on the duration of re-

sponse. Sequential combination chemotherapy was not associated with an increased incidence of severe side effects.

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DISCUSSION III: Chemotherapy of the Non-Hodgkin's Lymphomas [1,*]

Dr. Frei: I would like to ask the panel to comment on the importance of meningeal lymphoma as a cause of treatment failure during remission and whether current or prospective protocols are or will be addressed to this.

Dr. Anderson: Of our 200 patients with non-Hodgkin's lymphoma who entered complete remission, 81% of those who relapsed did so in lymph nodes. Meningeal lymphoma accounted for only 6% of relapses. Relapse was somewhat more frequent in patients with diffuse histiocytic and diffuse poorly differentiated lymphocytic disease. In summary, central nervous system relapse, as an isolated site of relapse, is not as frequent as we initially thought.

Dr. Bertino: We had no CNS relapses in our series of patients. This could be due to the high-dose methotrexate rescue program.

Dr. Bloomfield: Could you comment on age with respect to categories of non-Hodgkin's lymphoma and response?

Dr. Anderson: Within any histologic category, age did not make a difference in the ultimate remission rate or survival, which was roughly 10%.

Dr. Richardson: What is the long-term incidence of acute leukemia in patients in remission after treatment for non-Hodgkin's lymphoma?

Dr. Coltman: We and the National Cancer Institute have identified an increased risk of acute leukemia in patients with Hodgkin's disease, but this has not been demonstrated to date in non-Hodgkin's lymphoma. In Hodgkin's disease, the preponderant second malignancy has been acute leukemia.

Dr. Anderson: In our series we saw four instances of second malignancies in patients with nodular poorly differentiated lymphocytic lymphoma. One patient with a long history of cigarette smoking developed a large-cell anaplastic carcinoma of the lung about 7 years into his clinical course. The second developed a leiomyosarcoma of the buttock at a site where she had had a leiomyoma 2 years before entering therapy. A third patient with diffuse histiocytic lymphoma died of an ampullary carcinoma, and the fourth, who had had 8 years of single-agent chemotherapy before converting from nodular poorly differentiated lymphocytic lymphoma to diffuse histiocytic lymphoma, developed acute myelogenous leukemia 8 months after entering chemotherapy and 2 months after achieving complete clinical remission.

Dr. Frei: This is an older age group. Was the difference between the expected and the observed significant?

Dr. Anderson: No.

Dr. Dansker: Dr. Anderson alluded to a small group of patients in whom he recognized more than one histologic subgrouping of malignant lymphoma. Can the panel members tell us anything about the response to therapy and expected clinical course in these patients?

Dr. Anderson: As I mentioned, we put our patients in the less favorable category—there were only a small number and their survival was appropriate to that category.

Audience: What about the sequential or cyclic use of combinations of chemotherapeutic agents in non-Hodgkin's lymphoma?

Dr. Salmon: We studied this in patients with multiple myeloma. Such patients who had relapsed after alkylating agent treatment had second remissions induced with a combination of BCNU and adriamycin in 50% of patients. Similar results have been achieved by Bonadonna and others in non-Hodgkin's lymphoma. Thus, we are considering alternating non-cross-resistant combinations in future Southwest Oncology Group protocols.

Dr. Durant: Alternatively, one could use the second combination only in patients who relapse and are refractory to the initial combination.

Dr. Bonadonna: In preliminary studies, we have employed non-cross-resistant combinations in a cyclic fashion. Our initial complete remission rate and duration are not different from those in the classic combination chemotherapy approach.

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[1]The following investigators participated in this discussion: *E. Frei III* (chairman) (Sidney Farber Cancer Institute, Harvard Medical School, Boston, Mass); *T. Anderson* (National Cancer Institute, Bethesda, Md); *J. R. Bertino* (Yale University School of Medicine, New Haven, Conn); *C. D. Bloomfield* (University of Minnesota, Minneapolis); *Dr. Richardson* (Santa Rosa, Calif); *C. A. Coltman, Jr* (Wilford Hall US Air Force Medical Center, Lackland Air Base, San Antonio); *G. Dansker* (Philadelphia, Pa); *S. E. Salmon* (University of Arizona College of Medicine, Tucson); *J. Durant* (University of Alabama, Birmingham); *G. Bonadonna* (Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy); *F. Collanio* (Houston, Tex); *C. S. Portlock* and *S. A. Rosenberg* (Stanford University School of Medicine, Calif); *N. I. Nissen* (Finsen Institute, Copenhagen, Denmark); *G. Justice* (Letterman Army Medical Center, San Francisco, Calif); *P. Rosen* (Los Angeles, Calif); and *Dr. Johnston* (Minneapolis, Minn).

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Dr. Frei: Those of us who believe in the steep dose-response curve for antitumor agents consider the dose rate for a given treatment program to be highly important. I would like to point out that when one alternates two programs, the dose rate of each is substantially reduced.

Dr. Collanio: In order to further define risk factors, prognostic factors, and discriminants for treatment, we have performed a careful clinical pathologic correlative study. Prognostic variables have been defined and quantified, and an equation has been derived from which one can calculate the anticipated response rate. Such calculations correlate well with observed data. Using this approach and employing historical controls we have determined that the complete remission rate with the CHOP program is greater than that of COP.[2]

Audience: We have heard reports of six major studies today containing well over 1000 patients. Unfortunately, 3- and 5-year survival rates are not available except for one or two estimates from the Acute Leukemia Group B. Is there evidence that the higher complete remission rate with some of the more recent combinations results in improved survival at 3 or 5 years?

Dr. Portlock: As previous speakers have indicated, the risk of relapse from complete remission is very much influenced by the histopathologic type of lymphoma. Thus, several studies have indicated that for patients with diffuse histiocytic lymphoma, a complete remission which is confirmed by restaging is almost invariably durable. Thus, programs which provide an increase in remission rate might be expected to improve tumor-free survival. On the other hand, for most other types of non-Hodgkin's lymphoma, there is a continuing risk of relapse from complete remission. Thus, achieving a higher complete remission rate in such patients is an important goal, but major attention must be given to defining the nature and cause of relapse and to the treatment protocols addressed to this.

Dr. Nissen: Our 5-year survival is about 30% for unfavorable histologies and about 50% for favorable histologies.

Dr. Rosenberg: The complexities of non-Hodgkin's lymphoma and of the treatment programs presented and their results are major and must be particularly confusing to the physician in terms of what treatment to choose for a given patient. I would hope that Dr. Frei would attempt to summarize the status of the chemotherapy for non-Hodgkin's lymphoma. Among the problems, in addition to histologic classification, is the proportion of patients who were previously treated with the various protocols presented. What is the effect on response of previous treatment with a given modality? We need to know the criteria within the various studies for complete remission. This may range all the way from exquisitely documented re-staging to complete "clinical" remission. Our experience suggests that only about half of the clinical remissions are, in fact, complete remissions. In short, I plead for a careful, comparative analysis of the studies considering the above and additional factors so that the results in the various subgroups can be compared.

Dr. Justice: Dr. Bonadonna, you have successfully treated MOPP failures in Hodgkin's disease with ABVD.[3] Have you any experience with ABVD in non-Hodgkin's lymphoma?

Dr. Bonadonna: We did not use ABVD in non-Hodgkin's lymphoma but rather ABP.[4] This program is as effective as COP and non-cross-resistant in that a 50% response rate is achieved with ABP in COP-resistant patients.

Dr. Rosen: Dr. Anderson, you have reported a poor prognosis in patients with diffuse histiocytic lymphoma with marrow involvement. Also, you have reported that 29% of such patients develop meningeal lymphoma. What is your current therapeutic approach to patients with marrow involvement?

Dr. Anderson: We have not, as yet, developed a distinct regimen for these patients. In addition to the bone marrow involvement, gastrointestinal tract involvement is an adverse prognostic factor.

Audience: Would cytokinetic studies which would further define the proliferative thrust of the lymphoma aid in the strategy and tactics of treatment?

Dr. Frei: In general, cytokinetic studies involving in vitro incubation with thymidine and autoradiography have suggested a good correlation between the labeling index and the aggressiveness of the disease as measured by, for example, volume doubling time. Burkitt's lymphoma, for example, a highly aggressive tumor, has one of the highest labeling indices recorded (30%–40%). Such studies in patients with acute myelogenous leukemia have been of prognostic import and have led to altered treatment strategies. Such studies are important and are in progress in patients with lymphoma.

Dr. Johnston: Dr. Anderson, would you comment on the vigorous re-staging procedures? How might they influence treatment strategy?

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[2] CHOP = cyclophosphamide, adriamycin, vincristine, and prednisone.
COP = cyclophosphamide, vincristine, and prednisone.

[3] MOPP = mechlorethamine, vincristine, prednisone, and procarbazine.
ABVD = adriamycin, bleomycin, DTIC, and vinblastine.

[4] ABP = adriamycin, bleomycin, and prednisone.

Dr. Anderson: The recognition of minimal residual disease after completion of, for example, 6 months of combination chemotherapy is important. Thus, the presence of such disease indicates the need for further treatment either with the same program or a different one. The extent to which this will modify the duration of complete remission and survival remains to be determined.

Radiation Therapy of Localized Non-Hodgkin's Lymphoma[1]

R. S. Bush,[2,*] M. Gospodarowicz,[3] J. Sturgeon,[4] and R. Alison[4,5]

SUMMARY

The survival of 655 patients with non-Hodgkin's lymphoma was analyzed in an effort to define populations which can be cured by localized radiation therapy. In this paper, "cure" means that the survival of patients treated for lymphoma is the same as that of a similar but normal population of the same age distribution living during the same years. Patients with stage IA disease were shown to have a survival curve compatible with cure when treated with radiation therapy. However, patients with stage IIA disease had a higher mortality rate than the normal population out to 6 years, but cure could be demonstrated if patients with stage IIA localized were found to be free of disease at restaging using the criteria of Peters and Bonadonna. Consequently it is recommended that localized disease be defined as stage IA and IIA localized; in this group, which includes those with both nodular and diffuse disease, initial treatment by radiation therapy can be expected to give a high rate of survival over the long term. When treated with radiation in doses of 2500–3000 rads given in ten to 25 fractions, local control rates of >90% can be expected for all non-Hodgkin's lymphomas except those classed as diffuse histiocytic. The diffuse histiocytic lymphomas are more difficult to control and show no clear dose-response curve. Doses of 4000–5000 rads in 20–25 fractions can be expected to give 75% local control. Advanced lymphocytic disease showed no evidence of being curable by present methods, but approximately 30% of patients with advanced histiocytic disease do appear to achieve cure using chemotherapy with and without radiation therapy.

[Cancer Treat Rep 61:1129–1136, 1977]

Before the radiation therapy of localized lymphomas can be discussed, it must be decided whether treatment is being given with palliative or curative intent. This is particularly true at a time when chemotherapy is being used widely and Berard et al (1) have provided evidence that 40% of patients with advanced histiocytic lymphoma may have been cured with C-MOPP[6] (ie, no recurrences after 2 years in 40% of 122 patients who have been followed from 3 to 10 years). Consequently, the place of radiation therapy in the treatment of *localized* non-Hodgkin's lymphoma must depend upon its ability to cure. Localized disease then may be defined in terms of lesions that can be cured by radiation therapy given to a localized area. Also, by determining the fraction of patients cured, it may be possible to establish the relative roles of radiation therapy and chemotherapy in the treatment of non-Hodgkin's lymphomas.

To support these postulates, my colleagues and I reviewed data available from The Princess Margaret Hospital and also appropriate data from the literature.

[1]Supported in part by Public Health Service grant CA-19892 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

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[4]Department of Medicine, The Princess Margaret Hospital, Toronto, Ontario, Canada.

[5]The authors are grateful to Mrs. Isabelle Gamble for her tireless work in retrieving the charts to review and to members of the Department of Biostatistics, particularly Mrs. Joan Reid and Miss Theresa Chua, for their dedicated efforts. We also thank the Ontario Cancer Treatment and Research Foundation for financial support of this type of statistical review.

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[6]C-MOPP = cyclophosphamide, vincristine, prednisone, and procarbazine.

We will present evidence that localized lymphocytic and histiocytic disease can be eradicated in a large proportion of patients by using localized radiation therapy. This segment comprises approximately 20% of the total non-Hodgkin's lymphoma population. Advanced histiocytic disease also appears to be potentially curable, and the size of this cured group is about 10% of the total lymphoma population.

PATIENTS AND METHODS

Eight hundred and sixty-nine patients > 16 years old with the diagnosis of non-Hodgkin's lymphoma were seen at The Princess Margaret Hospital (PMH) between January 1, 1968, and December 31, 1973. Thirty-six charts could not be obtained for review (4%), and 214 patients had previously been treated elsewhere when they were first seen at the PMH and thus could not be included in this evaluation. The remaining 655 patients formed the basis of this study.

Staging was carried out retrospectively, using the criteria and recommendations for the staging of Hodgkin's disease derived from the Ann Arbor Conference (1971).

In 644 of the 655 patients available for study the original biopsy material was reviewed by Dr. T. C. Brown of PMH and classified by the criteria of Rappaport et al (2,3). The 11 patients in whom no pathology review was possible were kept in the study but their pathologic diagnosis is listed as "unclassified."

Patients lost to followup were classified as dead. No correction was made for death from extraneous causes.

Actuarial survival curves were determined from the date of diagnosis. Disease-free survival was determined from the date of diagnosis to the date of failure. The Kaplan-Meier tests for significance were used for comparison of survival curves.

In this discussion, "cure" is achieved when the survival curve for any patient becomes parallel to the normal survival curve. The latter has been obtained from *Statistics Canada* for a population of people in Ontario of the same age and sex distribution as the study population with lymphoma. To determine whether the study population survival curve was parallel to the normal survival curve, "relative" survival curves were calculated. By determining a relative survival curve, the survival is considered normal if it remains the same with time. This was the criterion used in the study; the relative survival curve, or the area enclosed by its 95% limits, became independent of time.

Concerning management policies in force at PMH during this period, patients with stage I and II disease were treated by radiation therapy directed to the involved site together with the adjacent or regional nodes. Patients with more advanced disease were treated in a variety of ways. Asymptomatic patients with nodular disease frequently received no treatment. Radiation was used in some symptomatic patients but more frequently chemotherapy was the treatment of choice—usually single- or two-agent therapy for nodular disease and a combination of three or more drugs for diffuse disease. The most frequent combination was cyclophosphamide, vincristine, and prednisone (CVP).

RESULTS

The distribution of the 655 patients by age and sex is similar to that in our previous reported series (4). The mean age was 58 years, and there were 365 men and 290 women.

Figure 1 compares the overall survival rate to the survival curve for normal people of the same age and sex distribution and to the survival of patients established in an earlier review (4). The curve is drawn on a semilogarithmic scale to demonstrate visually whether "cure" (5,6) has been achieved, that is, whether the rate of dying in the treated population is the same as in a normal population of the same age distribution living at the same time in Ontario. The survival curve for these 655 patients continues to have a steeper slope than the normal curve for the 6 years over which it is plotted; consequently, these data provide no evidence that a cure is being achieved. This conclusion is based on the assumption that, apart from the threat of the lymphoma, this group of patients would have the same survival as a normal population of the same age and sex distribution (7). Also there is no evidence that the rate of dying has changed from the 1962–1964 experience. The survival at any time after diagnosis is higher in this series than in the earlier study, but this improvement could be explained if a larger fraction of the patients in this study had been referred earlier in the disease or if later therapeutic methods had been more effective. The curve in the 1962–1964 series does become parallel to that of normal survival between 8 and 10 years at a time when between 20% and 25% of the earlier patients are still alive. Extrapolating this result back to 0 time indicates that the overall survival in this earlier experience is estimated to be approximately 30%. It is too early, however, to be able to demonstrate whether the curve of our later series (1968–1973) is going to flatten out at a higher level or at the same level.

The data represented in figure 1 should disturb the clinician if the object of treatment is cure. It should be remembered, however, that the survival curves of any group of patients may hide a subgroup(s) of patients who have been cured, and this includes those with localized disease treated by local radiation therapy as well as those who may have been cured with chemotherapy or by combinations of management methods.

To identify subgroups in whom the potential for cure might be demonstrated, we determined survival by stage (fig 2). Stage IA patients have a survival curve that is compatible with cure at 6 years, although we concede that a 15- or 20-year followup would be a better criterion. Stage IIA and IIIA patients are dying at a more rapid rate than the normal population (confirmed by calculating relative survival curves) and it can be shown that these deaths are due to disease and not complications of treatment. However, approximately 25% of patients with advanced disease also demonstrate a flattening of the survival curve, indicating that cure may be possible in this group as well. If it can be shown that this change in the curve is due to drugs, it could have important implications for the treatment of patients with lesser stage disease, particularly those treated predominantly with radiation.

To look further for characteristics that would identify truly localized disease, we determined the survival of those patients classified as having diffuse or nodular lymphoma. Figure 3 shows the survival of the 340 patients with diffuse disease. The slope of the curve does show a break although

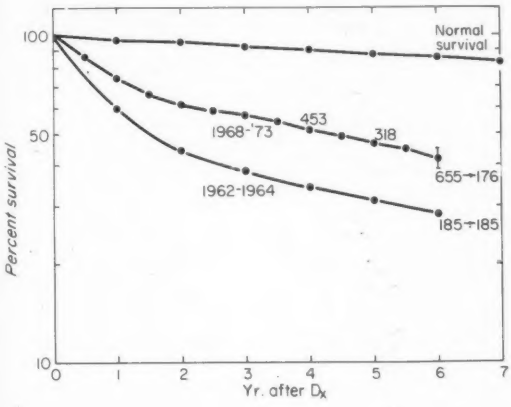

FIGURE 1.—Actuarial survival of all patients evaluated during this study compared with survival of a normal population of the same age and sex. Survival of patients from a 1962–1964 study (4) is also plotted.

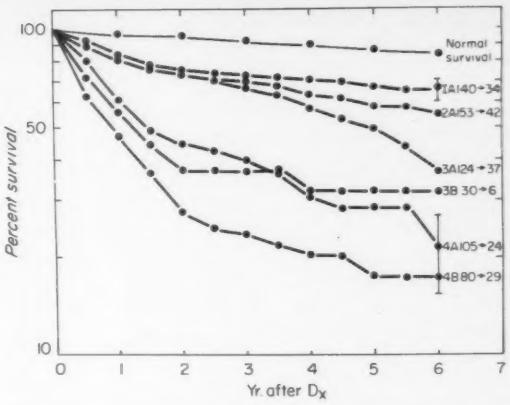

FIGURE 2.—Actuarial survival by stage (Ann Arbor system). 6 patients with stage IB with a 50% survival at 5 yrs and 17 stage IIB with a 22% 5-yr survival are not plotted on the graph because of their small numbers.

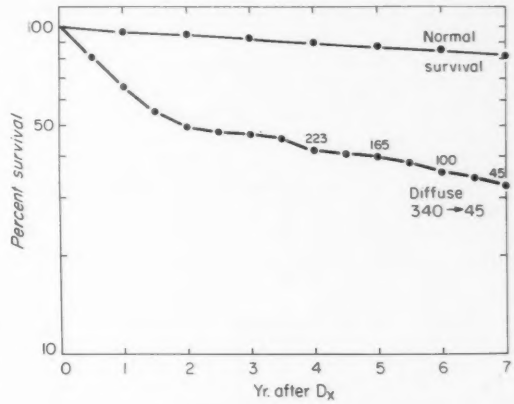

FIGURE 3.—Actuarial survival of all patients classified as having diffuse pathology, together with survival of a normal population.

the mean survival is only 2 years. Despite the break in the initial part of the survival curve, the tail of the slope does not become parallel to that of the normal survival curve, and thus, for the 7 years plotted, these patients are dying at a rate greater than normal. This finding suggests that the diffuse classification does not accurately select out a group of patients who may be cured, assuming that a population of patients is being cured.

Figure 4 shows the survival of the individual pathologic types within the diffuse classification. Patients with diffuse histiocytic disease have a survival curve that has a definite break in the

initial slope, but the survival of the patients with diffuse lymphocytic disease drops steadily with time—a trend which appears to contribute to the increased slope of the overall survival curve for all diffuse disease. The diffuse mixed and diffuse histiocytic undifferentiated groups are both small and no conclusions can be drawn about the slopes of the terminal parts of their survival curves.

Figure 5 shows the survival of the 305 patients with nodular lymphoma. The slope of this survival curve does not have a break in it, which indicates that the rate of dying is steady over the 7 years plotted. Such an exponential survival curve provides no evidence of cure although the mean period of survival is 5.75 years. This curve is consistent with the findings of Chabner et al (8), who showed that diffuse disease could be localized but nodular disease only rarely so. Because of the relatively gradual slope, it is possible that any flattening of the curve, which might demonstrate cure, requires a longer period than 7 years. Consequently, for periods up to 7 years and perhaps longer, any subgroup that might be cured by localized therapy may remain hidden.

In figure 6, which shows individual pathologic types within the nodular classification, it can be seen that the various groups, except nodular histiocytic, show the steady exponential loss of patients. The survival curve for the nodular histiocytic patients appears to be biphasic. This finding and the fact that the overall diffuse survival curve never becomes parallel to the normal survival curve strongly suggest that the pertinent classification

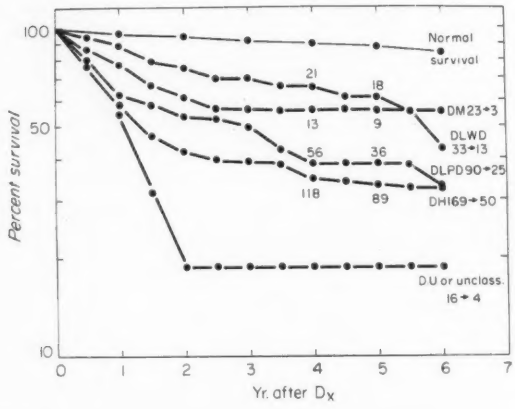

FIGURE 4.—Actuarial survival of the various subgroups of the diffuse classification. All stages are included. D = diffuse; H = histiocytic; M = mixed cell; LWD = lymphocytic well differentiated; LPD = lymphocytic poorly differentiated.

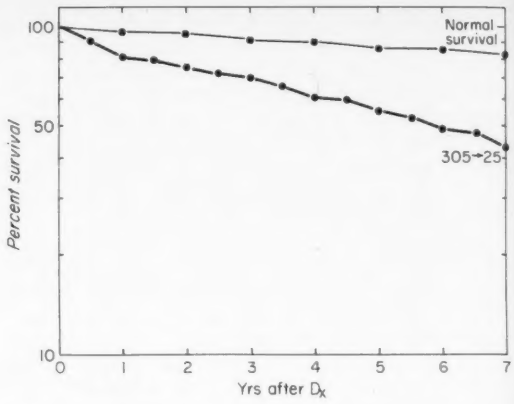

FIGURE 5.—Actuarial survival of all patients classified as having nodular pathology, together with survival of a normal population.

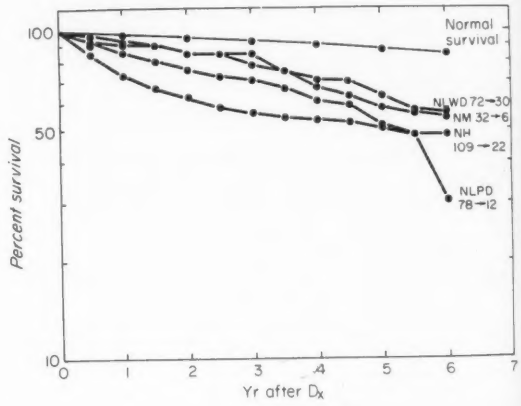

FIGURE 6.—Actuarial survival of the various subgroups of the nodular classification. All stages are included. N = nodular; H = histiocytic; M = mixed cell; LWD = lymphocytic well differentiated; LPD = lymphocytic poorly differentiated.

which will identify localized disease is *not* "diffuse" or "nodular." Consequently, we compared the survival curves for patients with histiocytic and lymphocytic disease to determine if this distinction would provide a clearer demarcation.

Figure 7 compares the overall survival for patients with histiocytic lymphomas with that for those with lymphocytic disease. As can be seen, these curves have a different shape; on the semilogarithmic plot the histiocytic is biphasic and the lymphocytic is linear. The shapes of the two graphs are different statistically at a P value of 0.002.

Figure 8 compares the survival curve for all histiocytic lymphomas with the normal survival curve. The overall survival curve for histiocytic disease becomes parallel to the normal curve between 5 and 7 years. The curves for both nodular and diffuse histiocytic lymphomas are biphasic and become parallel to the normal curve between 5 and 6 years, indicating that treatment has achieved survival compatible with cure. Thus both the nodular and diffuse histiocytic groups contain populations which are curable. By extrapolating the nodular histiocytic curve back to 0 time, it can be estimated that 60 patients (55% of the 109) have been cured. In the diffuse histiocytic patients, the same estimate suggests that 68 patients (40% of 169) would have been cured. Thus we estimate that 122 (46%) of the entire 278 patients with histiocytic disease may have achieved cure. What we cannot determine is how many of those cures were achieved in patients with localized disease treated by radiation therapy and how many resulted from chemotherapy.

Figure 8 also shows the survival of patients with mixed cell lymphoma, and although this survival is 55% at 6 years, it is not clear yet whether the curve will be exponential or biphasic.

In figure 9, those with mixed lymphoma are plotted with all patients with lymphocytic disease. The mixed lymphoma survival curve cannot be distinguished from the steady exponential loss shown by the overall lymphocytic curve and the various subgroups. Within the 6 years plotted, these data provide no evidence that patients with lymphocytic disease have been cured by the methods we used over the period 1968–1973. They indicate that most patients with lymphocytic disease may have generalized disease, and management by radiation, drugs, or combinations of these have not achieved cure. There may still be a subgroup which is curable, but because it is small or because the overall survival curve has such a gradual slope, it is still hidden at 7 years.

Continuing the search for localized lymphoma, survival rates were calculated by stage for nodal and extranodal presentations but, as figure 2 shows,

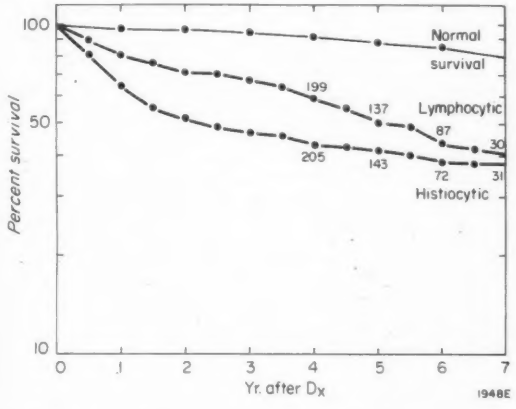

FIGURE 7.—Actuarial survival curves for all patients with either lymphocytic or histiocytic lymphoma compared to the normal survival curve. There were 278 patients with histiocytic disease and 226 with lymphocytic.

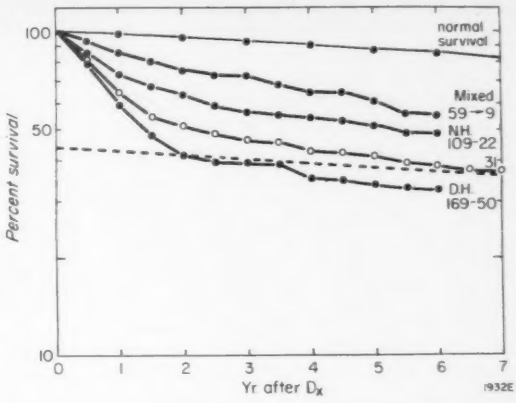

FIGURE 8.—Actuarial survival curves for patients with nodular histiocytic, diffuse histiocytic, or mixed cell lymphoma compared to normal survival curve.

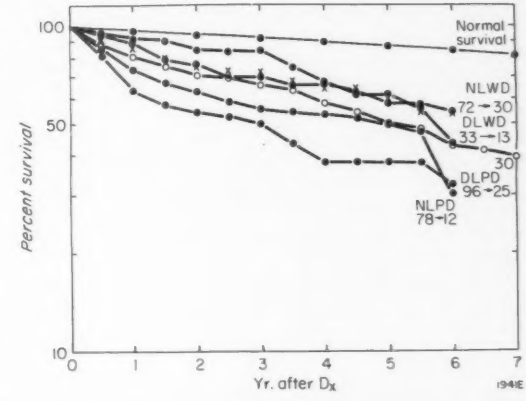

FIGURE 9.—Actuarial survival curves for patients with the various subclassifications of lymphocytic disease. Also plotted is the survival curve for mixed-cell lymphoma and normal survival curve.

only patients with stage IA disease appeared to have a survival curve compatible with cure. Consequently, we decided to examine the effect of subdividing stage IIA patients into those with "localized" and those with "extensive" disease. Other reports by Peters et al (4) and Bush and Ash (9) demonstrated that patients with stage II extranodal disease which has spread beyond the regional nodes had a significantly poorer survival than those in whom only regional nodes were involved. Banfi et al (10) proposed that, in non-Hodgkin's lymphoma the term "stage II" be limited to those in whom only two contiguous regions were involved. Using these criteria for extranodal and nodal lymphoma, we determined the survival of patients with stage IA and IIA (localized) disease treated by radiation therapy.

All three survival curves in figure 10 become parallel to the normal survival curve. Dropping from the calculation those with extensive stage IIA disease removes patients who are dying within the first 6 years at a rate higher than normal. As a result, we have concluded that the Ann Arbor staging is not satisfactory in non-Hodgkin's lymphoma, and that the staging limitation suggested previously by Peters, Bush, and Banfi appears to define prognosis more accurately. The survival curve of the 192 patients with stage IA and localized stage IIA lymphocytic and histiocytic disease treated by radiation therapy extrapolates back to 0 time at the 75% point; thus, 144 of these patients with localized disease have a survival at 6 years which is compatible with cure.

To determine whether these 144 patients have been cured by radiation therapy only, we calculated the disease-free survival in this group (fig 11). As can be seen, the failure-free survival curves for both the patients with lymphocytic and those with histiocytic disease are compatible with cure, but they are about 20% lower and are parallel to the survival curve. This result means that half of the 40% who failed have been controlled by further therapy, while the remaining 115 (60%) have a disease-free survival rate that is the same as that of the normal population.

These 115 patients represent 20% of the 586 with lymphocytic and histiocytic disease who were seen and evaluated. The same proportion of those with localized mixed cell lymphomas could be considered cured, so that radiation therapy of localized disease is seen to provide cure for 20% of the total population of non-Hodgkin's lymphomas.

Table 1 shows that local control was achieved in those patients with stage IA and IIA disease in whom evaluation was possible. Because of the range in the fraction size used, nominal single dose values were not calculated. The size of the fractions ranged from 100 to 250 rads/fraction. These data, however, indicate that with 2500–3000 rads in ten to 30 fractions local control is possible in 90% of all non-Hodgkin's lymphomas, except those with diffuse histiocytic disease. Increased size of a mass implies that a further increase is necessary in the total dose. As Fuks and Kaplan (11) have previously reported, diffuse histiocytic lymphoma showed a lower frequency of local control than the other lymphomas. Patients with stage IA diffuse histiocytic lymphoma had a 90% complete response rate and a 76% local control rate, but those with stage IIA disease had only a 71% complete response rate.

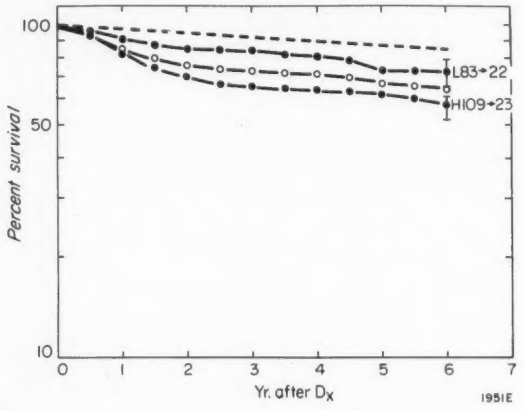

FIGURE 10.—Actuarial survival of patients with stage IA and "localized" stage IIA disease treated by radiation therapy. *See* text for description of the term "localized."

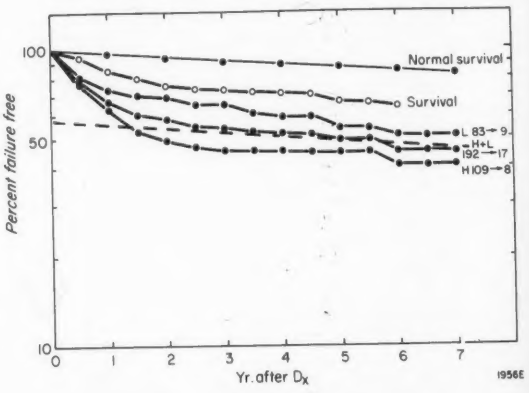

FIGURE 11.—Failure-free survival of patients with stage IA and "localized" stage IIA disease treated by radiation therapy.

TABLE 1.—Fractions of patients by pathologic types controlled at different doses of radiation

Dose (100–250 rads/fraction)	No. of patients with local control/No. evaluable			
	All lymphocytic	All mixed cell	Nodular histiocytic	Diffuse histiocytic
< 2000	0/1			0/2
2000–2499	11/13	2/2	2/3	1/2
2500–2999	17/18	3/3	9/9	2/2
3000–3499	24/26	7/8	15/16	6/10
3500–3999	17/18	6/7	7/10	13/20
4000–4499	7/8			7/8
4500–5000				3/3
5000+				

The local control rate was only 58% in stage IIA patients.

DISCUSSION

Survival remains the most reliable measurable indication of the efficacy of any given treatment, particularly if survival can be measured in terms of cure. In light of current knowledge of the management of non-Hodgkin's lymphoma, this present study set out to measure the effect of radiation therapy in localized lymphoma in terms of cure. Despite the enthusiasm aroused by the responses to chemotherapy in advanced disease, cure can be demonstrated only in histiocytic disease. We estimate that in this series of patients with advanced histiocytic disease only about 30% have been cured. However, the precise contribution of drugs and radiation to this survival has not been analyzed. This 30% of patients with advanced histiocytic disease represents about 10% of all patients evaluated.

Radiation therapy in localized histiocytic lymphomas achieves a complete response rate of approximately 85%. In the presence of this high percentage of complete responses, the local recurrence rate was 25%. The remaining failures were due to progression of disease outside the treatment volume or to metastatic disease. We have no good evidence that very high doses improves the control rate, because about 25% of histiocytic lymphomas appear to be resistant to present radiation fractionation practices. It is unlikely that larger radiation fields and consequently lower doses would bring about major improvement. The maximum control rate so far achieved with chemotherapy is 40% (1) compared with an irradiation control rate of 75% when the radiation field encompasses the disease. Consequently, irradiation still must be considered the treatment of choice for accurately staged localized histiocytic lymphoma, although careful prospective studies to evaluate the rate of control of chemotherapy in patients with less bulky disease may modify this point of view.

Should chemotherapy be combined with radiation therapy in the treatment of localized histiocytic lymphoma? Bonadonna and his colleagues (12), who did an early analysis of such a study, found no improvement in disease-free survival for patients with histiocytic lymphoma. There was an improvement for lymphocytic lymphomas although maximum followup was only 3 years. Our results suggest that this improvement may be only temporary and will not manifest itself in a final analysis of cure. The Stanford group (13) could demonstrate no improvement when patients with unfavorable histology were treated with total nodal irradiation followed by a combination of drugs (CVP) with or without bleomycin. It should be pointed out that the failure-free curve for stage IA and localized stage IIA histiocytic patients is parallel but 15% below the survival curve. Thus, 30% of those patients who failed initial radiation were controlled with further treatment and the final result is similar to the control achieved in patients with advanced histiocytic disease. This pattern of management spared 50% of the irradiated patients from chemotherapy or wider field irradiation. However, the use of both radiation and drugs may be justified in patients with inadequately staged diffuse histiocytic lymphomas.

Lymphocytic disease which is localized also appears to be curable. Our patient material provides no evidence yet that systemic management improves the cure rate. Consequently, it seems logical to treat patients with apparently local disease by radiation alone because there was no local recurrence of disease in > 90% of these patients.

At present we recommend that mixed cell lymphomas be grouped with histiocytic lymphomas, because they have a pattern of survival which may be demonstrating cure.

It should be emphasized that although this anal-

ysis has focused on the effects of radiation therapy in localized non-Hodgkin's lymphomas, we believe radiation also has an important part to play in the treatment of more advanced disease.

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Team Approach to Management of Non-Hodgkin's Lymphomas: Past and Present [1]

Lillian M. Fuller,* Jess F. Gamble, James J. Butler, Joseph G. Sinkovics, Sidney Wallace, Richard G. Martin, Edmund A. Gehan, and C. C. Shullenberger [2]

SUMMARY

A detailed review of our results of radiotherapy for stage I and II non-Hodgkin's lymphomas has been presented as background for our current multidisciplinary approach which uses multiple-agent chemotherapy, radiotherapy, and immunotherapy for nodular and diffuse stage I, II, and III lymphomas of the poorly differentiated lymphocytic, mixed, and histiocytic varieties. Optimum management is based on coordinated efforts of medicine, radiotherapy, pathology, diagnostic radiology, and surgery. In stage I, II, and III disease, routine staging procedures include lymphangiography, bilateral iliac crest needle biopsies of the bone marrow, and percutaneous needle biopsies of the liver. Staging laparotomy is considered essential to our present program for stage I, IE, II, and IIE disease. In our opinion, staging laparotomy is not indicated in stage III or IIIE disease. Although very preliminary, results for these programs are encouraging. This paper presents the concept of team management and a specific plan for its implementation.

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The optimum management of lymphomatous diseases is facilitated by a program which incorporates the major disciplines routinely involved in the investigation and care of the patient. At the M. D. Anderson Hospital these include medicine, radiotherapy, pathology, diagnostic radiology, and surgery. Our team approach to management of non-Hodgkin's lymphomas is based on: (*a*) the correlation of Rappaport's classification (1) with the natural history of stage I, IE, II, and IIE patients following intensive irradiation of involved regions in the upper torso and total abdominal irradiation for lower-torso disease (2); (*b*) a systematic approach to the initial investigation and all subsequent evaluations for documentation and staging of disease; and (*c*) the progressive development of effective multiple-agent chemotherapy programs in the Southwest Oncology Group (SWOG).

Before the general implementation of Rappaport's histopathologic classification, information on the non-Hodgkin's lymphomas was generally uninterpretable because of conflicting terminology (table 1). Although the medical profession associated a diagnosis of "giant follicle lymphoma" with an indolent course, the prognostic significance of less well-developed tumor nodules was not recognized.

To correlate the natural history of non-Hodgkin's lymphoma with Rappaport's classification, slides were reclassified for 226 stage I, IE, II, and IIE patients admitted between 1961 and 1969. Approximately half of these patients were staged clinically; the others were staged after lymphangiography. The incidence of presenting sites for nodal (stages I and II) and extranodal (stages IE and IIE) disease is depicted in figures 1–3 for nodular and diffuse lymphomas of the lymphocytic, mixed, and histiocytic varieties. Regardless of the classification of the malignant cell or the stage of the disease, the majority of extranodal presentations were classified as diffuse lymphomas. Extranodal presentations of the head and neck and the upper gastrointestinal

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TABLE 1.—Terminology of non-Hodgkin's lymphomas

Lymphoblastoma	Lymphosarcoma Brill-Symmers disease Giant follicle lymphoma Follicular lymphoblastoma	I. Non-Hodgkin's lymphomas A. Nodular (follicular) 1. Lymphocytic, poorly differentiated 2. Mixed 3. Histiocytic 4. Undifferentiated
Lymphocytic	Lymphosarcoma Lymphocytoma	B. Diffuse 1. Lymphocytic *a.* Well-differentiated *b.* Intermediate differentiated *c.* Poorly differentiated *d.* Poorly differentiated, convoluted
Lymphoblastic	Lymphosarcoma Lymphoblastic	2. Mixed
Clasmatocytic stem cell	Reticulum-cell sarcoma	3. Histiocytic 4. Undifferentiated *a.* Burkitt's *b.* Non-Burkitt's
		C. Other 1. Mycosis fungoides 2. Malignant histiocytosis 3. Lennert's lymphoma

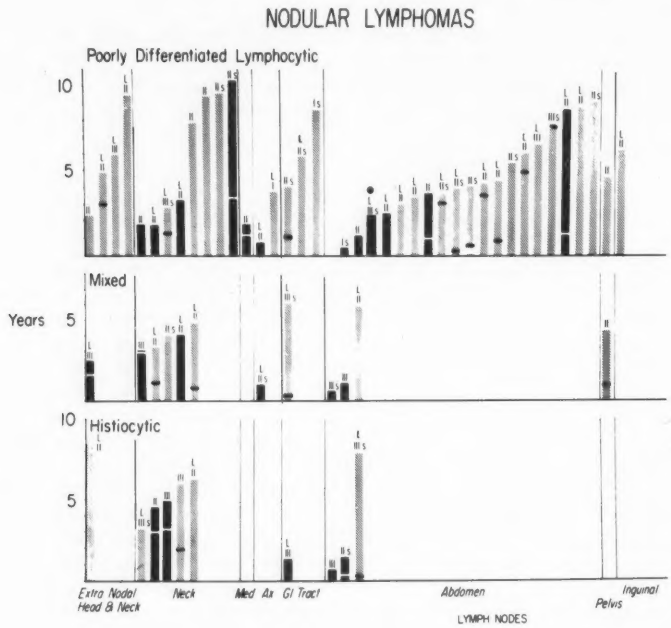


FIGURE 1.—Nodular lymphomas, stages I and II. Relative incidence and duration by apparent origin. Each bar represents one patient; black bars represent dead patients. A break in a bar indicates the time of initial relapse. One patient lost to followup was omitted. Neck = cervical nodes; Med = mediastinal nodes; Ax = axillary nodes; abdomen, pelvis, and inguinal = apparent primary adenopathy in these sites; I, II, and III = well-defined, intermediate, and poorly defined nodules; S = sclerosis; L = lymphography for staging; ● = dead from other causes (*from* ref 2).

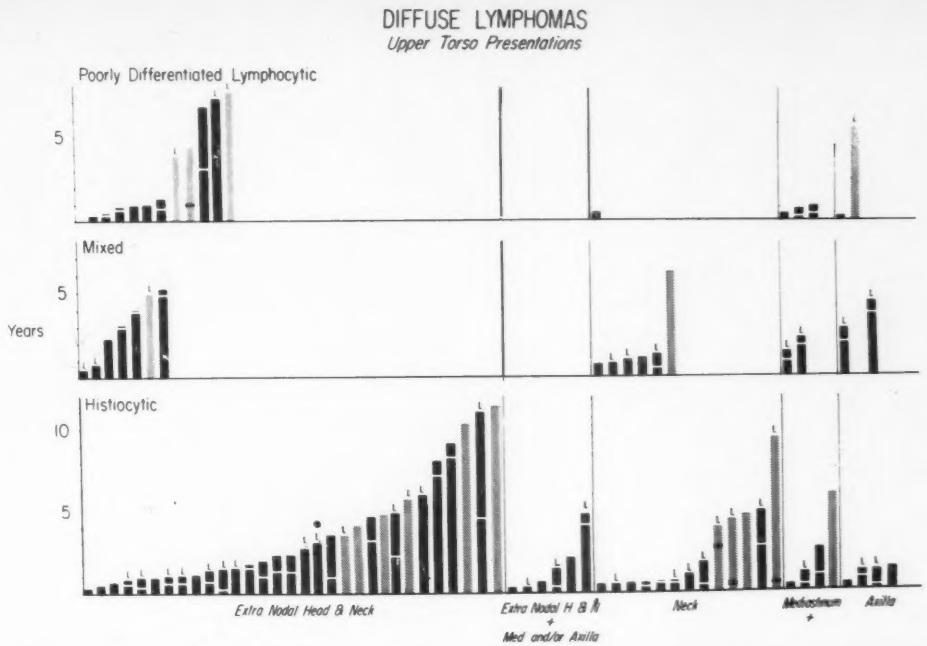


FIGURE 2.—Poorly differentiated lymphocytic, mixed, and histiocytic diffuse lymphomas, stages I and II. Relative incidence and duration by apparent origin of upper-torso presentations. Mediastinum, axilla, and neck apply to lymph node sites (compare with fig 1); ● = dead from other causes (*from* ref 2).

tract accounted for approximately 50% of the diffuse group. Waldeyer's ring was involved in approximately two thirds of the patients with extranodal presentations limited to the head and neck. Other sites were paranasal sinuses, gingivobuccal sulcus and surrounding structures, the thyroid gland, and the orbit (3). In the lower torso, the incidence of extranodal presentations was stomach and small bowel, 20, and testicle, five.

RADIOTHERAPY

Most of the 226 patients were treated with cobalt 60 irradiation. In the upper torso, treatment was limited to the affected regions. Prophylactic treatment was not given to adjacent areas, except in stage I presentations limited to Waldeyer's ring, the upper neck, or the thyroid gland. For patients with stage I disease involving Waldeyer's ring or the upper neck, the treatment fields included Waldeyer's ring, both sides of the neck, and the supraclavicular fossae. Prophylactic treatment in these cases was based on the observation that approximately 70% of patients with involvement of Waldeyer's ring presented with cervical adenopathy. Because of the tendency for malignant lymphoma of the thyroid to spread to the neck and mediastinum, these structures were routinely included in the radiation fields for all thyroid presentations. Treatment of all other stage I extranodal disease was limited to the involved region because, in our earlier experience (3), subsequent spread to the neck had been rare.

Regardless of the involvement, upper-torso disease was generally treated at a tumor dose of 1000 rads/week. The total dose depended both on the presentation and the response of the tumor. Because of the limited tolerance of the mediastinal contents and the spinal cord, treatment of mediastinal presentations was generally limited to a maximum tumor dose of 4000 rads calculated in the midplane of the upper mediastinum. The dose to the lower mediastinum was somewhat less. Based on previous observations that extranodal presentations in the head and neck were generally more resistant, a policy evolved to treat most of these cases with a minimum tumor dose of 5000 rads. Residual disease was given additional treatment through reduced fields whenever possible.

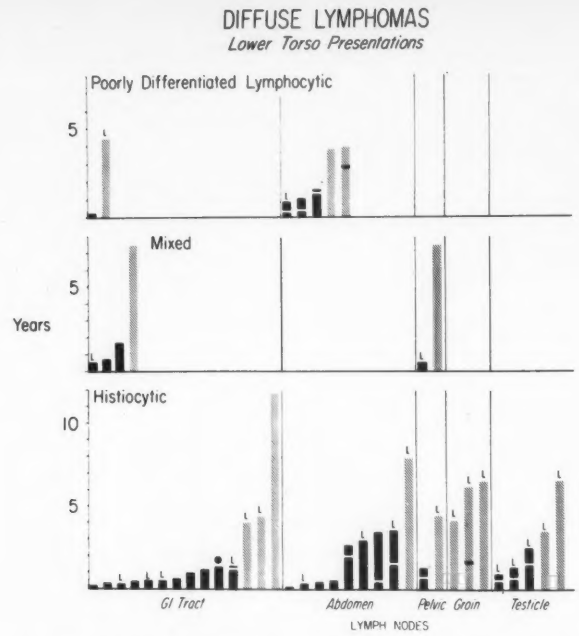


FIGURE 3.—Poorly differentiated lymphocytic, mixed, and histiocytic diffuse lymphomas, stages I and II. Relative incidence and duration by apparent origin of lower-torso presentations. Abdomen, pelvic, and groin apply to lymph node sites (compare with fig 1); ● = dead from other causes (*from* ref 2).

Lower-Torso Presentations

Between 1961 and 1969, our treatment policy for lower-torso presentations, other than for stage I disease of the testicle, was to administer intensive irradiation to the entire abdomen, including the pelvis and femoral regions. This decision was based on unsatisfactory results achieved in intensive treatment of palpable disease with low-dose irradiation (4). Preliminary experience with treatment to the entire abdomen and pelvis in a single course demonstrated that this approach was not suitable for all patients because of poor general tolerance or a drop in the wbc or platelet count below levels of 2000/mm^3 and 60,000/mm^3, respectively. To correct this problem, the decision was made to treat the upper two thirds of the abdomen and pelvis in series, whenever possible. This approach allowed for a rest interval of 6–8 weeks between courses of treatment for recovery of the wbc and platelet counts. Currently, total abdominal irradiation, administered in one course, is reserved for patients with extensive disease in both the upper two thirds of the abdomen and the pelvis. Whether the abdomen and pelvis were treated together or in series, radiotherapy was administered at a tumor dose of 750 rads/week for a total of 3000 rads. When possible, additional treatment was given for residual disease. Treatment to both the upper two thirds of the abdomen and the pelvis was delivered through equally loaded parallel opposed, anterior, and posterior fields. To avoid overdosage, the kidneys were shielded posteriorly with 2 HVL of lead from the beginning of treatment. The liver was not shielded. Although radiation hepatitis was not a problem in this series, sporadic cases occurred in patients treated with a combination of chemotherapy and radiotherapy. Our current policy for patients programmed to receive multiple-agent chemotherapy and radiotherapy is to shield the right lobe of the liver with 1 HVL of lead during treatment to the anterior field.

Results of Treatment With Radiotherapy

Survival curves were calculated according to the method of Kaplan and Meier (5). Gehan's modification of the generalized Wilcoxon test was employed to evaluate differences between survival curves (6). The overall 5-year survival rate for patients with

nodular lymphoma was 65% versus 26% for patients with diffuse lymphomas (fig 4).

Nodular Lymphomas

Permanent local control was achieved in approximately 80% of all upper-torso presentations. Although the local control rate was lower for abdominal presentations, 60% was considered relatively satisfactory in view of the large number of cases with massive disease. Regardless of differences in local control for upper- and lower-torso presentations, 5-year survival figures were not statistically different for these two categories of lymphangiogram-staged patients (fig 5). No statistically significant difference was demonstrated in 5-year results of 71% and 52% for lymphangiogram-staged versus clinically staged patients, respectively. This latter group included a large number of cases with lower-torso presentations whose stage would not have been altered by lymphangiography (fig 6). Finally, the effect of histology on survival approached significance. For the poorly differentiated lymphocytic variety, the 5-year survival figure was 74% versus 50% for the mixed ($P = 0.09$) and 46% for the histiocytic ($P = 0.17$) varieties (fig 7).

The incidence of new disease, which generally presented in the lymph nodes on the opposite side of the diaphragm, was related to histology. At the time of this analysis, the overall incidence of progression was 57% for poorly differentiated lymphocytic disease versus 76% and 70% for the mixed and histiocytic types, respectively. Regardless of management, the effect of progression on survival appeared to be more serious for patients whose disease presented above the diaphragm. Of 17 patients with upper-torso presentations who developed

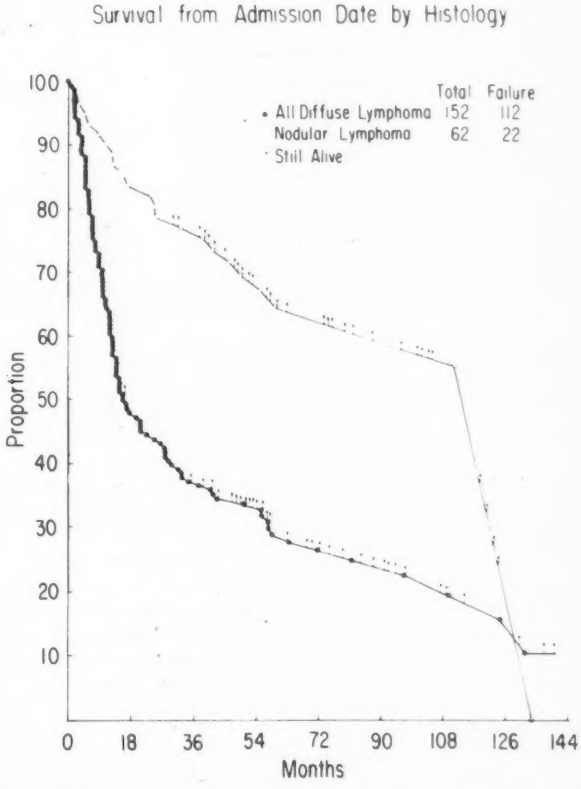


FIGURE 4.—Comparison of survival curves for all nodular vs diffuse lymphomas. In calculating survival curves for this study, patients who died of other causes with no evidence of lymphoma were counted as alive, whereas patients who were lost to followup were counted as dead from lymphoma. Differences in survival curves for total group of nodular and diffuse lymphomas demonstrate superior prognosis for the nodular pattern (*from* ref 2).

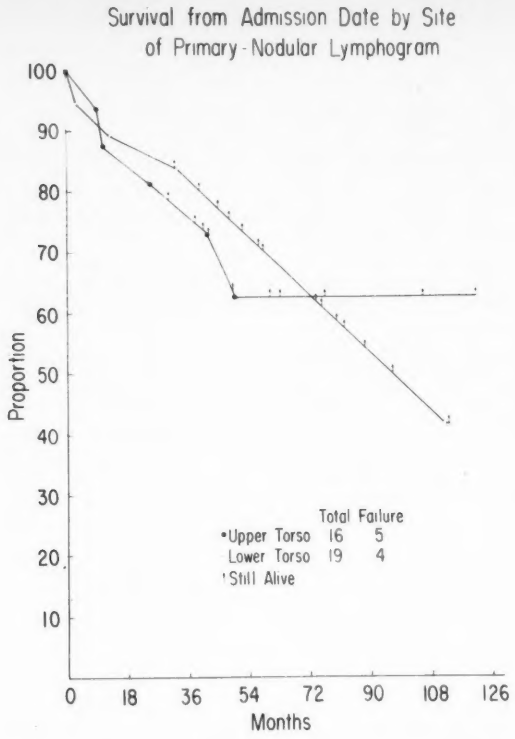


FIGURE 5.—Survival curve for nodular lymphoma, lower- vs upper-torso presentations staged after lymphangiography. No significant differences are noted in the 5-yr survival figures for upper- and lower-torso presentations, ie, 62% vs 70% (*from* ref 2).

new manifestations, only five are surviving. By contrast, 12 of 22 patients with lower-torso disease who experienced progression are alive.

Diffuse Lymphomas

Differences in survival figures for poorly differentiated lymphocytic, histiocytic, and mixed-cell types of diffuse lymphomas were not statistically significant (fig 8). Although the effect of lymphangiography as a staging procedure was significant, an improvement in the 5-year survival figure from 16% to 33% was disappointing.

Despite the poor overall survival figures, local control for upper-torso presentations of the diffuse lymphomas was approximately the same as for the nodular lymphomas. In the lower torso, control depended on the mode of presentation. As anticipated, local control of inguinal or testicular disease was the same as for disease in the upper torso. By contrast, 64% of patients with abdominal or pelvic presentations had persistent or recurrent local disease. In general, these patients had massive adenopathy and/or unresectable disease in the upper gastrointestinal tract or the cecum.

In the histiocytic series, the number of extranodal cases was large enough to permit us to determine its influence on survival. For the upper torso, survival figures for stage IE and IIE disease at 5 years were 38% and 16%, respectively (fig 9). Combined results for stage I and II nodal presentations in the upper torso were 16%.

In the lower torso, information was not available for precise staging of all presentations. However, we compared stage I and II patients with disease limited to lymph nodes and stage IE and IIE patients whose disease involved extranodal sites. Five-year survival figures of 35% and 30%, respectively, were not statistically different (2).

Patterns of spread were similar for all histologic subtypes of diffuse lymphomas. Regardless of the initial presentation, diffuse dissemination was the most common primary manifestation of progression. In 71 patients with histiocytic lesions who developed new disease, 37 had diffuse dissemination as the

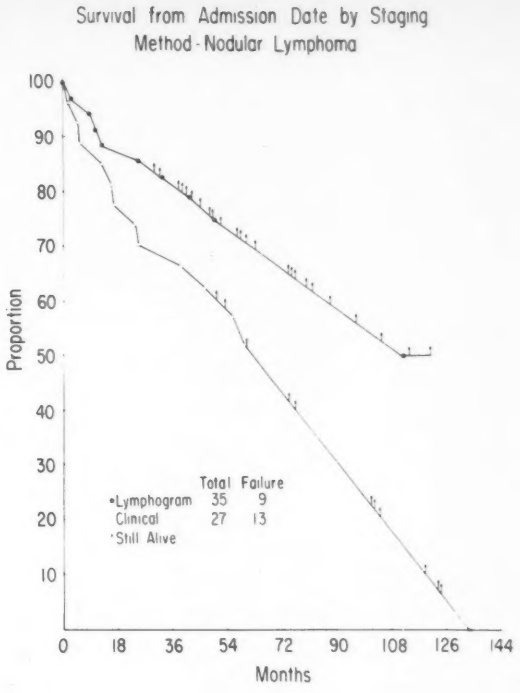


FIGURE 6.—Survival curves for lymphangiogram- and non-lymphangiogram-staged patients with nodular lymphoma. Nodular lymphoma patients staged after lymphangiography had a median survival of 112 mos; patients staged without benefit of lymphangiography had a median survival of 63 mos. Although the difference in the curves was not statistically significant, note that in both groups approximately 50% of the patients had lower-torso presentations (*from* ref 2).

first manifestation. Leukemia was the first evidence of new disease in four patients; three of these had poorly differentiated lymphocytic lymphomas and slides on the fourth patient were interpreted as diffuse lymphoma of the mixed-cell type. Leukemia was not a primary manifestation of progression in any of the children in this series who were admitted with a diagnosis of undifferentiated lymphoma. Although treatment of progression was generally disappointing, a few long-term remissions were induced with chemotherapy and/or radiotherapy (2).

CHEMOTHERAPY

Since 1970, the chemotherapy of stage III and IV diffuse lymphomas has progressed rapidly. Proof that single agents were of limited value in the diffuse lymphomas led to the development of effective multiple-agent programs (7). In a study conducted by the SWOG, a combination of cyclophosphamide, vincristine, and prednisone (COP) produced complete response rates of 50% in "lymphosarcoma" and 39% in "reticulum-cell sarcoma" (8).[3] In this program, maintenance chemotherapy produced some increase in remission duration in lymphosarcoma. The addition of adriamycin[4] to the COP

[3] Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate.

Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1).

Prednisone: NSC-10023; CAS reg. No. 53-03-2; pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-.

[4] Adriamycin: NSC-123127; CAS reg. No. 23214-92-8.

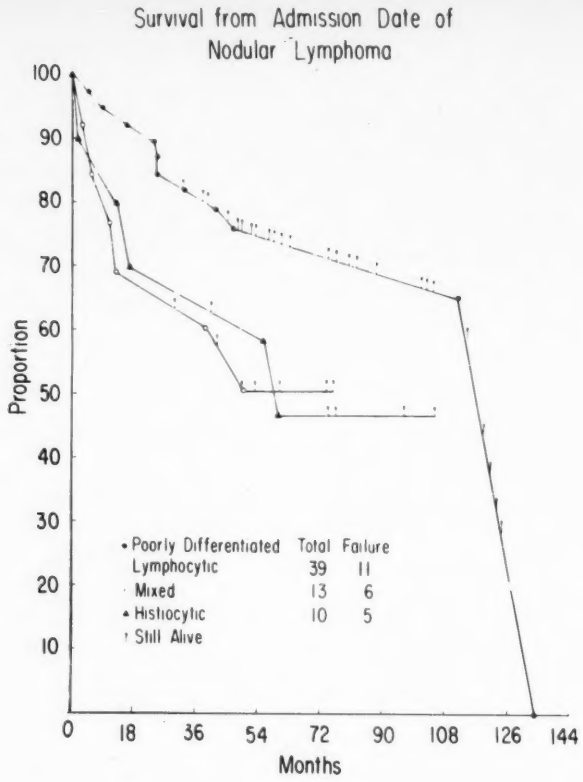


FIGURE 7.—Comparative survival for poorly differentiated lymphocytic, mixed, and histiocytic nodular lymphomas. Patients in poorly differentiated lymphocytic group had a somewhat better survival than patients in the other 2 groups. However, the differences are not statistically significant at the 0.5 level (*from* ref 2).

program (CHOP) achieved complete remission rates > 60% in both lymphosarcoma and reticulum-cell sarcoma without prohibitive toxicity. At the present time, the median duration of remission for this program is > 2 years (9). A preliminary report of a program which includes bleomycin (CHOP-Bleo)[5] describes 80% complete remissions.

Although combination chemotherapy has produced a dramatic increase in the complete remission rate in generalized disease, the median duration of remission is less satisfactory. Young et al (10) have shown that the initial relapse tends to occur in the original sites of disease. Maintenance programs did not increase the relapse-free interval appreciably in early programs. Whether maintenance chemotherapy and/or immunotherapy will improve the relapse-free interval in patients treated with CHOP still has to be determined.

NEW APPROACHES TO TREATMENT

The correlation of Rappaport's classification with both survival and disease-free survival has demonstrated that in stage I and II disease involved-field radiation is insufficient treatment in either the nodular or the diffuse varieties of non-Hodgkin's lymphomas (2,3,11). In developing more effective treatment, not only for stages I and II but also for stage III disease, we built on past experience by devising clinical trials to determine the value of additional systemic therapy for patients treated with involved-field radiotherapy for stage I and II disease, and the value of radiotherapy added to multiple-agent chemotherapy in stage III disease (9).

[5] Bleomycin: NSC-125066; CAS reg. No. 11056-06-7; [2,4'-bithiazole]-4-carboxylic acid, 2'-(2-aminoethyl)-, monohydrate.

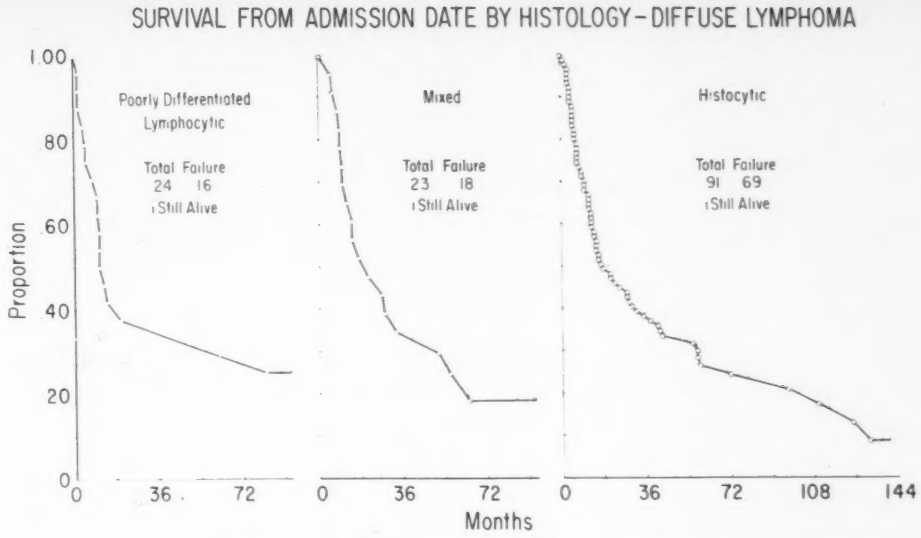


FIGURE 8.—Survival curves for histiocytic, mixed, and poorly differentiated lymphocytic lymphomas. Comparative 5-yr survival figures were 22% for mixed, 26% for histiocytic, and 29% for poorly differentiated lymphocytic (*from* ref 2)

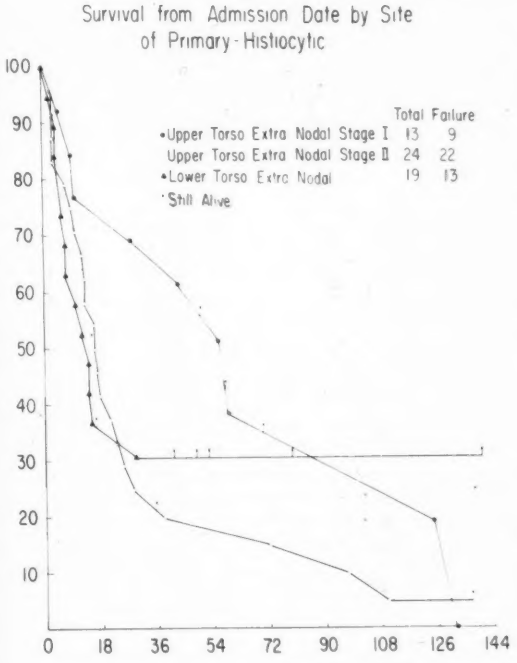


FIGURE 9.—Survival curves for extranodal stage IE vs IIE upper-torso presentations and for combined group of stage IE and IIE lower-torso presentations of diffuse lymphomas (*from* ref 2).

Stages I and II

In considering systemic therapy, we decided to compare the SWOG chemotherapy combination, CHOP-Bleo, with an immunotherapy combination of bacillus Calmette-Guérin (BCG) (12) and lymphoma viral oncolysate (13,14) in a randomized clinical trial (fig 10). To determine the value of adjunctive systemic therapy as precisely as possible in patients with apparently localized disease, this program requires exploratory laparotomy and splenectomy for staging in lymphangiogram-negative patients, except for those with lower-torso presentations who have other evidence of abdominal disease. Such patients are staged after percutaneous liver biopsy and bilateral iliac crest, and bone marrow biopsies. Because of our previous experience that local control was poor in those with diffuse histiocytic lymphoma who had more than minimal abdominal disease, such patients were excluded from this protocol. Details and results of this protocol will be described in a subsequent publication.

Stage III

Although stage III lymphoma represents advanced disease, the lesions are confined to regions amenable to prolonged control or even possible "cure." In nodular lymphomas, because disease tends to be confined to lymphatic areas for long

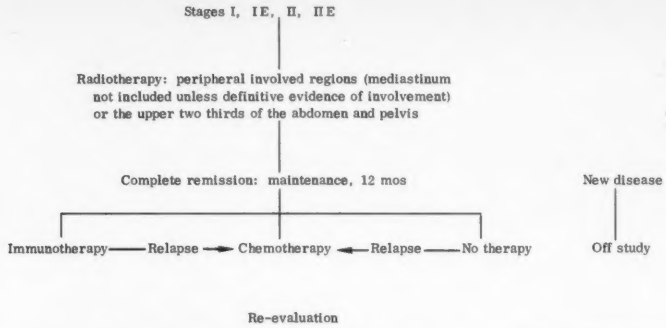


FIGURE 10.—Basic design for management of stage I, IE, and IIE non-Hodgkin's lymphomas excluding stage II and IIE diffuse histiocytic with massive intra-abdominal involvement (*see* table 4 for chemotherapy and text for immunotherapy).

periods, the major emphasis is placed on radiotherapy. Because disease in the abdomen is usually extensive, total abdominal irradiation is used for all stage III patients with nodular lymphoma. Initial and interval low-dose chemotherapy (table 2) is used for reduction of tumor load and consolidation after remission is achieved by radiotherapy.

In the diffuse lymphomas, because of the tendency for hematogenous dissemination, high-dose chemotherapy (table 3) is used for remission induction. Interval radiation to limited fields is used to prevent relapse in original sites of disease. This program was tailored to meet the specific requirements for each of three major stage III clinical presentations: massive or extensive abdominal disease, minimal abdominal disease, and extranodal head and neck disease involving the upper respiratory and/or digestive passages (table 4). Life-threatening head and neck disease demands emergency treatment with radiotherapy and further investigation of the extent of other disease is deferred. If subsequent staging laparotomy (in a negative lymphangiogram-staged patient) results in a stage III classification, the protocol regimen is resumed. Because of limitations of bone marrow reserve associated with intensive chemotherapy, radiotherapy for abdominal disease is limited to involved areas only.

Because we believed that further chemotherapy would not be well tolerated, it was not considered for maintenance therapy. However, we thought immunotherapy might be of value for maintenance in patients with limited bone marrow reserves. To determine whether maintenance treatment was even necessary, and if so, whether a combination of non-specific immunotherapy with BCG and specific immunotherapy with lymphoma viral oncolysate was of value, patients in complete remission were randomized to no further treatment versus immunotherapy.

Preliminary Results in Stage III Disease

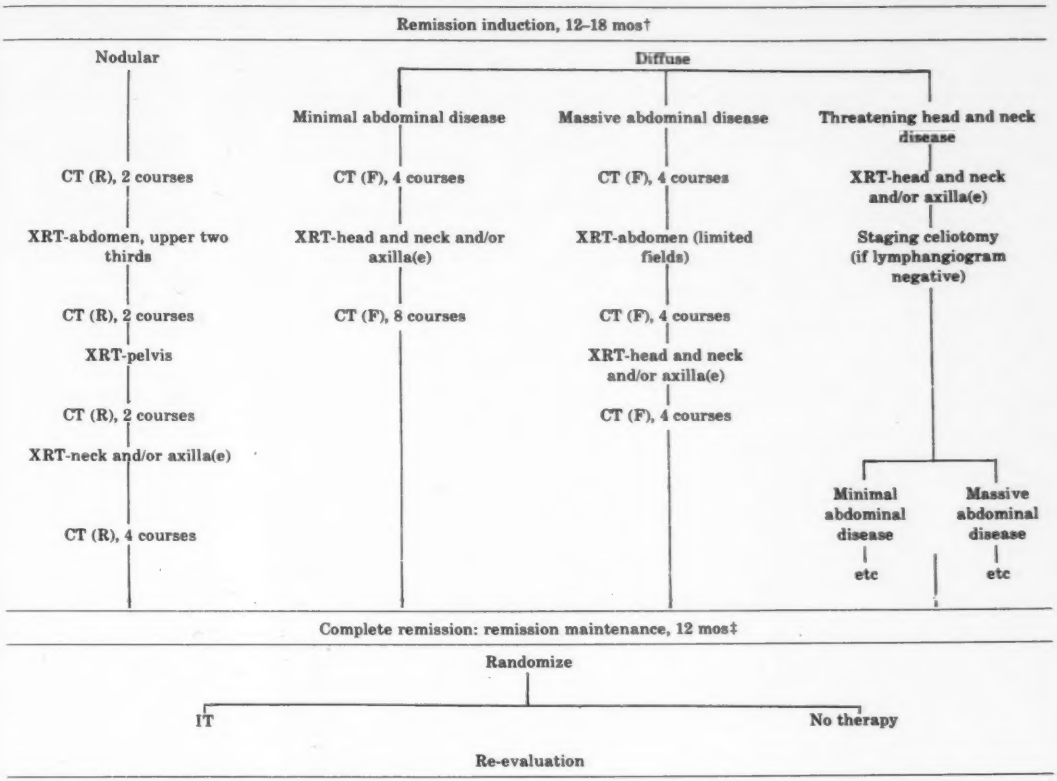
Nodular lymphomas.—As of April 1976, 16 stage III patients with a diagnosis of nodular lymphoma had been entered in this study. To date, 11 patients, most of whom have completed all prescribed therapy, are surviving free of all clinical evidence of disease 6–22 months after admission. One patient is surviving with disease at 13 months. Two patients are dead at 6 and 10 months. Toxicity was a problem in only one patient.

Diffuse lymphomas.—One laparotomy and ten lymphangiogram stage III patients with a diagnosis of diffuse histiocytic lymphoma have been followed for 6–20 months after admission. Of these, nine are free of clinical evidence of disease. One patient with disease at 9 months had only partial remission while receiving chemotherapy. One patient is dead at 12 months. Toxicity was a problem in one patient. In addition to the 11 stage III patients who were treated on this protocol, five stage I and II patients with a diagnosis of diffuse histiocytic lymphoma presenting in the abdomen were treated on this protocol. By definition, these patients were excluded from the stage I and II protocol. These patients are surviving free of disease 5–19 months after admission.

DISCUSSION AND CONCLUSIONS

In the past, patients with stage I and II non-Hodgkin's lymphomas were treated primarily with involved-field radiotherapy. Patients with stage III

TABLE 2.—Basic design for management of stage III and IIIE non-Hodgkin's lymphomas (including stage II diffuse histiocytic with massive intra-abdominal involvement)*



*See tables 3 and 4 for details of systemic therapy.
†XRT = radiotherapy; CT = chemotherapy; IT = immunotherapy; R = reduced dose; F = full dose.
‡Failures and partial responders go off study.

TABLE 3.—Schedule for reduced-dose CHOP-Bleo induction therapy for nodular lymphomas—courses of chemotherapy repeated at 3–4-wk intervals (*see* table 2)

Drug	Dose (mg/m²/route)	Schedule
Cyclophosphamide	600/iv	Day 1
Adriamycin	35/iv	Day 1*
Vincristine	1.4/iv	Day 1
Prednisone	40/oral	Days 1–5
Bleomycin	5/iv	Day 1

*Stopped at 450–550 mg/m² or 450 mg/m² if patient receives irradiation to mediastinum.

TABLE 4.—Schedule for full-dose CHOP-Bleo—courses of chemotherapy repeated at 3–4-wk intervals (*see* table 2)

Drug	Dose (mg/m²/route)	Schedule
Cyclophosphamide	750/iv	Day 1
Adriamycin	50/iv	Day 1*
Vincristine	1.4/iv	Day 1
Prednisone	40/oral	Days 1–5
Bleomycin	5/iv	Day 1

*See footnote to table 3.

and IV disease were treated with chemotherapy. Results of this approach were confusing until 1973, when a joint effort was made to correlate response in stage I and II disease with Rappaport's classification.

As a result of clarifying the natural history of these diseases, it became apparent that new approaches to treatment were needed and a more organized effort must be made to achieve maximum benefit from those disciplines routinely involved in the investigation and care of these patients.

Preliminary to discussing possible new approaches, interested members from the departments of medicine, radiotherapy, pathology, diagnostic radiology, and surgery organized a weekly planning clinic to ensure joint participation in the management of all new patients. As a result of the deliberations of this clinic and more formal conferences, new programs were developed. Although the weekly planning clinic was begun to establish the diagnosis, stage, and treatment of all new lymphoma patients, it also provided a ready exchange of new information and made possible mutual education. During the clinic, deliberations of the staff are recorded for each patient, and the case is coded for eventual computer analysis.

In our institution, the weekly planning clinic has greatly facilitated interdepartmental communication which has resulted in improved patient care. In our opinion, institutions involved in the management of any significant number of lymphoma patients can only benefit by instituting a team approach to management, data analysis, and the eventual development of new approaches to treatment.

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Total-Body Irradiation in the Treatment of Lymphocytic Lymphoma[1]

John T. Chaffey,[2,*] Samuel Hellman,[2] David S. Rosenthal,[3] and William C. Moloney[3]

SUMMARY

Seventy-eight patients with advanced lymphocytic lymphoma have been treated by total-body irradiation (TBI) since 1969. Fifty-one of these patients received TBI as their initial and only primary therapy, and of these, 36 had a nodular histology and 15 had a diffuse histology according to the Rappaport classification. Treatment consisted of 15 rads twice weekly to 150 rads total dose. Persistent local tumors were given local boost irradiation. None of these 78 patients experienced significant morbidity; toxicity was confined to thrombocytopenia, and in 40% of the patients treatment was administered over a prolonged course to allow platelet recovery. Of the 51 patients who received TBI as primary treatment, 80% achieved a complete response for a median relapse-free survival of 24 months and an actuarial 5-year survival of 68%. TBI is an effective therapy in advanced lymphocytic lymphoma and produces long remissions without maintenance in many patients. It should be considered a systemic agent, and its use in combination with chemotherapeutic agents deserves further investigation.

[Cancer Treat Rep 61:1149–1152, 1977]

Non-Hodgkin's lymphomas constitute a group of diseases which show great variety in clinical presentation and prognosis. Unlike Hodgkin's disease, improved methods of evaluating the extent of the disease have not led to significant improvements in treatment and survival. Fundamental differences of opinion regarding pathologic classification still exist among experienced pathologists (1,2). However, it is widely accepted that histologic nodularity usually indicates a less aggressive process than the diffuse forms of histology. This report has used the Rappaport classification (1); all cases discussed in this paper are in the category of non-Hodgkin's, non-histiocytic lymphoma.

Clinically, the vast majority of patients with lymphocytic lymphoma present with disseminated disease and, following diagnostic evaluation, < 10% have apparently localized disease (3,4). Since the major therapeutic decision appears to lie between the treatment of apparently localized disease versus systemic disease, exhaustive diagnostic evaluation generally is not indicated once the physician has established that the disease is disseminated.

In the small minority of patients with truly localized (stage I) disease, radiation therapy (and occasionally surgery) may provide effective control, giving an 82% 5-year actuarial survival in our experience, and a similar survival in the experience of other investigators (4–6). In patients with widespread lymphoma, aggressive combination chemotherapy has met with only limited success, in contrast to Hodgkin's disease (7,8).

Total-body irradiation (TBI) has been used as a systemic antitumor agent since the early 1900s. In the 1930s Heublein, at Memorial Hospital in New York, demonstrated a doubling of survival time in patients with disseminated non-Hodgkin's lymphoma treated with TBI (9). With the development of systemic chemotherapeutic agents in the 1940s, this technique was discontinued, and interest in the technique of TBI was not regenerated until 1970 when Johnson et al (10) presented data suggesting its efficacy.

Following Johnson's encouraging report, we started a program of therapy employing TBI in

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late 1969. Portions of this experience have been previously reported (11,12). This report will summarize our current experience in treating 78 patients from November 1969 to December 1975; 51 of these patients were previously untreated.

Patients were staged by clinical examination, liver function tests, bone marrow biopsies, and, in most cases, lymphangiography. Laparotomy is not routinely used for staging at our institutions and was performed in only six patients in this series.

On the basis of diagnostic evaluation, patients with abnormal lymph nodes above and below the diaphragm were considered to have stage III disease. Patients with significant bone marrow infiltration or evidence of visceral involvement were categorized as having stage IV disease. Exhaustive attempts to distinguish between stage III and IV disease were not made because this did not affect our therapy.

Treatment was delivered on a 4-MeV linear accelerator and patients were given 15 rads twice a week until 150 rads were delivered or until hematopoietic depression limited or protracted the treatment. Doses were calculated at the midplane of the pelvis and the patient was treated from the side and turned midway through treatment. Dosimetric studies using thermoluminescent dosimeters indicated a 40% increase in dose in the region of the neck, or approximately 21 rads per treatment session with a relatively uniform dose throughout the truncal area. Patients with persistent local tumors were given "boost" irradiation to these areas to a dose of 1000–2000 rads. Since most patients had generalized disease, "boosts" were necessary in only a minority of patients.

Blood studies were obtained before each treatment, and treatment was withheld if the platelet counts were falling rapidly. Both the absolute platelet level and the rate of decline were considered when determining whether to continue treatment. In general, treatment was suspended when the platelet counts fell to $< 40{,}000/mm^3$ or if the platelet counts fell $> 50\%$ in 1 week to levels $< 100{,}000/mm^3$. In 40% of the patients the treatment course was interrupted or modified because of low platelet counts. The actual doses delivered ranged from 105 to 210 rads in a single course.

Patients treated can be divided into three groups. The first group consisted of 51 previously untreated patients, all stage III or IV, 16 of whom had diffuse histology and 35 of whom had a nodular pattern. The second group consisted of 21 patients who had received prior systemic chemotherapy ranging from several months of single-agent therapy to extensive combination chemotherapy. All of these patients had stage IV disseminated disease and had failed

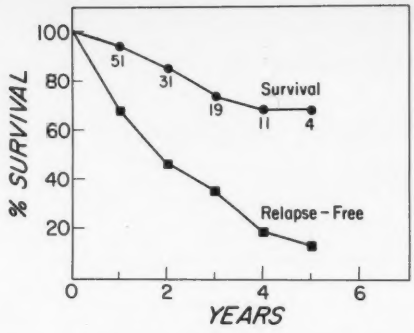

FIGURE 1.—Survival and relapse-free survival in 51 patients following TBI.

to improve on chemotherapy. A third group of six patients received TBI as adjuvant systemic therapy in addition to localized irradiation for stage I or II non-Hodgkin's lymphoma. Currently, these six patients are all free of disease at periods ranging from 6 to 42 months, but will not be considered further because their response to TBI cannot be separated from that to localized irradiation. In the group of patients with advanced disease and no previous therapy, none were treated until there was evidence of disease progression. Survival in these patients is scored from the beginning of treatment.

Figure 1 shows the results of treatment in the 51 previously untreated patients. The survival rate is 68% at 5 years; however, relapse-free survival dropped to 13%. It remains to be seen whether there will be a small subset of patients remaining in relapse-free survival, and if so, it is important to identify this group before treatment. Currently, two patients are living in relapse-free status > 5 years after TBI treatment. Figure 2 gives a comparison of the distribution of nodular versus diffuse histology in these patients. Patients with nodular lymphoma have an 80% 5-year survival while those with diffuse histology manifest a considerably lower survival. However, the number of patients free of relapse is small in both groups, suggesting that although survival is better for nodular histologies, most patients eventually relapse. Stages could not be shown to influence either the relapse-free status or survival; therefore, we have considered stage III and IV patients together.

Toxicity in the previously untreated patients was confined to bone marrow depression. There was no nausea, alopecia, weakness, or malaise. However, all patients developed a relative thrombocytopenia and, as a result, therapy was temporarily suspended in more than one third. In four patients the platelet

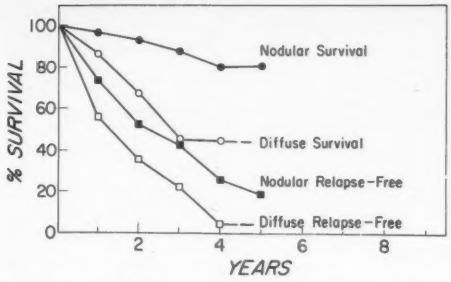

FIGURE 2.—Survival and relapse-free survival with nodular versus diffuse histology.

count fell to ≤ 15,000/mm³ and treatment was stopped at 90–105 rads. Two patients demonstrated bone marrow infiltration by lymphoma. A third had a negative bone marrow biopsy, yet continued to be thrombocytopenic for many months. The platelet count nadir was generally reached 10 days to 2 weeks after completing the course of TBI. In 40% of the evaluable patients the platelet counts fell to < 40,000/mm³ shortly after the completion of treatment. After treatment, the platelet counts usually rose rapidly toward normal. Although the major toxicity was thrombocytopenia, the leukocyte counts were also depressed but rose promptly following treatment. In these patients, the extent of the hematologic depression could not be correlated either with the age or stage of disease. Some patients showed minimal alteration in hematologic parameters; in one patient the dose was carried to 210 rads without significant hematologic depression.

The 21 patients with extensive previous therapy are more difficult to analyze. These patients exhibited such a variety of clinical courses and therapies that quantitative evaluation is impossible. Most of them had reached an end stage in the clinical course of their lymphoma and were refractory to all chemotherapy. The doses delivered ranged from 15 to 120 rads and most patients received 60–90 rads. Only two patients demonstrated a complete response, eight demonstrated a partial response, and eight showed no improvement following TBI alone but responded when additional local irradiation was given. Three patients were preterminal and died after one or two treatments only. The duration of remissions in patients with extensive previous therapy was very short; only two patients maintained remission for > 2 months before relapsing again. Thus, it appears that TBI is not an effective secondary therapy for patients failing with other modalities of treatment.

Four patients who failed following TBI at periods ranging from 8 to 18 months were given a second course of TBI. All of these patients achieved a complete response; however, the duration of remission was shorter than that following the first course of treatment and all patients subsequently required drug therapy. Thrombocytopenia persisted in one patient. A second patient developed a preleukemic phase and then progressed to an erythroleukemia and died at 34 months. While the other two patients maintained long remissions following their second course of TBI, both have ultimately required chemotherapy for relapse. On the basis of this experience, we do not believe it is desirable to re-treat patients with TBI since thrombocytopenia may persist and such treatment may increase the likelihood of secondary leukemia.

Earlier, in order to test our treatment against systemic chemotherapy, we compared the initial 25 patients treated in these series with a group matched by age, sex, and pathologic sub-group. They were treated with cyclophosphamide, vincristine, and prednisone (COP) and were seen at our institutions by the same physicians in the immediately preceding period (7). These chemotherapy patients were selected from a larger group in an attempt to match as closely as possible the important variables of the disease. Figure 3 demonstrates an updated survival curve for these two groups. While these curves show no statistical difference, the TBI patients seem to do at least as well and possibly have some therapeutic advantage. It is our opinion that TBI offers patients with stage III and IV nodular lymphocytic and mixed lymphoma the opportunity of a complete remission for an extended period with far less toxicity than with combination chemotherapy.

The majority of the patients treated by TBI as initial management have now relapsed and have required secondary therapy with either bleomycin,

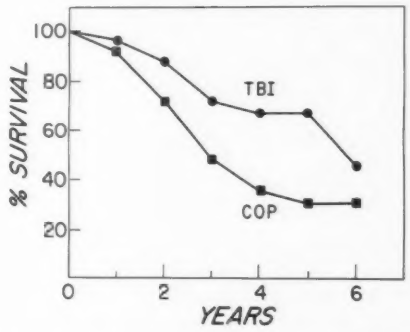

FIGURE 3.—Survival comparison between matched pairs treated with TBI versus combination chemotherapy (cyclophosphamide, vincristine, and prednisone).

.iophosphamide, vincristine, and prednisone (B-·OP); bleomycin, adriamycin, cyclophosphamide, vincristine, and prednisone (BACOP); or the single agents, chlorambucil or cyclophosphamide. The choice of chemotherapy has been individualized, depending on the aggressiveness of the patient's disease and the tolerance he has exhibited. We have encountered no significant difficulties in administering chemotherapy to patients who had received TBI earlier, if ≥ 3 months had elapsed. Since the median time to relapse is 24 months, patients enjoy, on the average, 2 years of life without any therapy before they require some form of systemic chemotherapy.

In choosing treatment one must balance therapeutic effectiveness against the price paid in morbidity and toxicity. Advanced nodular lymphocytic lymphoma responds to a variety of treatment regimens, none of which is yet curative. Furthermore, in this group of diseases characterized by a long and variable natural history, we cannot yet choose the best therapy from among several alternatives ranging from localized to generalized irradiation and from single-agent chemotherapy to aggressive combination chemotherapy (13,14). We believe that TBI offers a high probability of complete remission for an extended period with a minimum of morbidity and toxicity for the patient. When relapse occurs, secondary chemotherapy can be given effectively. It is possible that more effective regimens could be developed by combining TBI with other systemic chemotherapy to produce more durable remissions than are presently obtainable by any therapy. It may be that by shielding portions of the bone marrow during TBI, toxicity could be decreased without any loss of therapeutic efficacy. These considerations will require further investigation, but ultimately may lead to a more effective combination therapy for this varied and challenging spectrum of lymphomatous disease.

LIST OF COMPOUNDS

Adriamycin: NSC–123127; CAS reg. No. 23214–92–8
Bleomycin: NSC–125066; CAS reg. No. 11056–06–7; [2,4'-bithiazole]-4-carboxylic acid, 2'-(2-aminoethyl)-, monohydrate
Chlorambucil: NSC–3088; CAS reg. No. 305–03–3; butyric acid, 4-[*p*-[bis(2-chloroethyl)amino]phenyl]-
Cyclophosphamide: NSC–26271; CAS reg. No. 6055–19–2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate
Prednisone: NSC–10023; CAS reg. No. 53–03–2; pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-
Vincristine: NSC–67574; CAS reg. No. 2068–78–2; leurocristine, sulfate (1:1)

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Advanced Lymphocytic Lymphoma: Randomized Comparisons of Chemotherapy and Radiotherapy, Alone or in Combination [1]

Robert C. Young,* Ralph E. Johnson, George P. Canellos,[2] Bruce A. Chabner, Harmar D. Brereton, Costan W. Berard, and Vincent T. DeVita [3]

SUMMARY

Ninety-nine previously untreated patients with stage III and IV malignant lymphoma were randomized to receive either cyclic combination chemotherapy (50 patients) or extensive "systemic" radiotherapy (49 patients). Histologic classification included nodular poorly differentiated lymphoma (54 patients), nodular mixed lymphoma (21 patients), and diffuse poorly differentiated lymphoma (24 patients). High overall response rates were seen with either approach (90% for radiotherapy; 86% for chemotherapy) and complete remissions were relatively common (60%–80%). Overall median survival of all patients in this trial will exceed 5 years regardless of the induction therapy used; however, disease-free survival is not commonly achieved with either regimen. Relapse-free survival rates at 4-year followup, regardless of induction regimen, are 13% for diffuse lymphomas and 24% for nodular lymphomas. The second prospective trial attempts to use a combined approach and compares cyclic combination chemotherapy with total-body irradiation and combination chemotherapy. Initial results on 34 patients indicate high overall response rates (100%) and similar complete remission rates (64%–67%). With 14 months' median followup no patients in either arm of the trial have died but relatively equal numbers have relapsed.

[Cancer Treat Rep 61:1153–1159, 1977]

Extensive staging procedures from several institutions have established that a majority of patients with non-Hodgkin's lymphoma (NHL) have disseminated disease at the time of initial presentation (1–3). This observation has been given further support by the known high frequency of systemic relapse following radiotherapy for apparently localized disease (4). These and other observations have made it apparent that whatever modality is selected for primary therapy for most patients, the approach requires some form of systemic therapy.

In recent years combination chemotherapy programs have been used for primary management of NHL and have resulted in generally higher complete remission (CR) rates than single-drug therapy for many, but not all, histologic types (5–10).

Chemotherapy has not been the only systemic approach effective in advanced NHL management. In parallel with the studies of single-agent and combination chemotherapy, the treatment of advanced NHL using fractionated doses of total-body irradiation (TBI) was being investigated (11–13). These initial studies, which have been confirmed (14,15), indicate that small fractional doses are well tolerated and produce CR in a large number of patients treated.

In 1968, we initiated a randomized prospective trial to compare cyclic combination chemotherapy with extensive radiation therapy, including TBI, in the treatment of stage III and IV lymphocytic lymphoma. As of September 1974, 99 patients had been randomized and were evaluable. On the basis of that initial trial, a second trial was initiated in

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September 1974, comparing combination chemotherapy with TBI and chemotherapy. The results of the first trial and the preliminary information from the second study are the subject of this presentation.

PATIENTS AND METHODS

Ninety-nine consecutive patients with previously untreated advanced (stage III and IV) NHL entered the trial between 1968 and 1974 and were randomized to receive either combination chemotherapy (50 patients) or radiotherapy (49 patients). The characteristics of the patient groups are shown in table 1. The Ann Arbor staging classification was used throughout and all histologic material was classified by the Rappaport system (16,17). The clinical and pathologic information on each patient was evaluated at a multidisciplinary lymphoma staging conference before randomization. Initial stratification included only the stage, but histology was added later in the trial.

TABLE 1.—Patient characteristics

	Chemotherapy		Radiotherapy	
Patients	50		49	
Sex (M/F)	21/59		25/24	
Median age (range)	46 (23–72)		50 (27–67)	
Histology				
Nodular	42		33	
NPDL	29		25	
Mixed	13		8	
Diffuse (DPDL)	8		16	
Stage		*(% total)*		*(% total)*
III	13	(26)	15	(31)
IV_L	5	(10)	11	(22)
IV_M	9	(18)	5	(10)
$IV_{L,M}$	19	(38)	14	(29)
IV_{other}	4	(8)	4	(8)

All biopsy material was obtained and reviewed in the Laboratory of Pathology, NCI, and a diagnosis was rendered to conform with the Rappaport classification before entry in the trial. At the completion of the trial, all of the material was re-examined and reclassified without knowledge of the initial treatment assignment or the clinical outcome. This accounts for the imbalance of nodular and diffuse histologies randomized to each treatment group. The histologic subgroups are shown in table 1. The trial included all of the nodular (NPDL) and diffuse poorly differentiated lymphocytic (DPDL) lymphomas. Excluded from this trial were undifferentiated lymphoma, Burkitt's lymphoma, and diffuse histiocytic or mixed lymphomas.

Routine staging procedures were used throughout the trial and have been detailed elsewhere (1,5). In addition, sequential nonsurgical and surgical staging procedures were used to establish final Ann Arbor staging. The details of this sequential staging approach have been published previously and are described elsewhere in this issue (1,18). The final stage of the patients in the present study is shown in table 1.

TREATMENT PROGRAMS

Chemotherapy (50 Patients)

Two chemotherapy regimens were used, depending upon the histologic type. All patients with lymphocytic lymphomas (NPDL, DPDL) received the cyclophosphamide, vincristine, and prednisone (CVP) regimen, and patients with nodular histiocytic or those with nodular mixed lymphocytic-histiocytic lymphomas received the cyclophosphamide, vincristine, procarbazine, and prednisone (C–MOPP) regimen. The details of the regimens, including doses, sliding-scale modifications, toxicities, and results in other patient populations, have been published previously (5,9,19–21). A dose reduction was employed for hematologic depression and the dose of both vincristine and prednisone was modified for the nonhematologic toxicity unique to these agents. Both regimens were administered cyclically at 21- (CVP) or 28-day (C-MOPP) intervals until a CR was obtained. Two additional cycles of chemotherapy were administered after clinical CR before systematic restaging was undertaken. Staging procedures short of major surgery were repeated to assess the site and volume of residual disease, if any. If there was microscopic or other evidence of residual disease at any site, six more cycles of chemotherapy were administered before restaging. CR indicates disappearance of all evidence of disease and return to a normal performance status. Patients achieving CR were given no further therapy until evidence of relapse. Partial remission (PR) was defined as (1) $> 50\%$ decrease of measurable disease for a minimum of two cycles; (2) regrowth of measurable disease after complete clinical regression within 6 weeks off therapy; and (3) complete peripheral remission but persistence of microscopic lymphoma in the bone marrow and/or liver after ≥ 12 cycles of chemotherapy. Patients with PRs continued to receive intermittent therapy until CR was achieved or evidence of progressive disease developed.

TABLE 2.—Treatment by histologic subgroup

Histology	Chemotherapy		Radiotherapy					
	No. of patients	Therapy	No. of patients	TNI	TNI + whole abdomen	TBI + TNI or involved field	TBI	TBI (hemi-body)
DPDL	8	CVP	16			2	7	7
NPDL	29	CVP	25	4	2	4	6	9
Nodular mixed	13	C-MOPP	8	2	3		2	1
Totals	50		49	6	5	6	15	17

Radiotherapy (49 Patients)

The radiotherapy consisted of three general techniques. Eleven patients with stage III disease received total-nodal irradiation (TNI) to tumor doses of 2060–3600 rads given in 2–4 weeks. In these instances ports were modified to include Waldeyer's ring, epitrochlear nodes, and the low femoral nodes. Five of these 11 patients had whole-abdominal irradiation as well because of extensive mesenteric adenopathy and/or liver involvement.

The other 38 patients were treated with TBI using one of two techniques. Twenty-one patients received TBI delivered in fractions of 10 rads/fraction to alternate sides of the body to a total dose of 150–300 rads. The other 17 patients received hemibody irradiation of 50 rads/day to the upper or lower half of the body with an intervening rest period of 8–12 weeks to a total dose of 300–600 rads. Five of the patients receiving TBI received supplemental local irradiation of lymph node or bony lesions (2000–3000 rads) after completion of TBI. The total radiation dosage administered was variable and was left to the discretion of the therapist. The total duration of therapy varied from 3 to 5 months.

In contrast to the restaging procedures outlined for the chemotherapy patients, biopsy restaging for

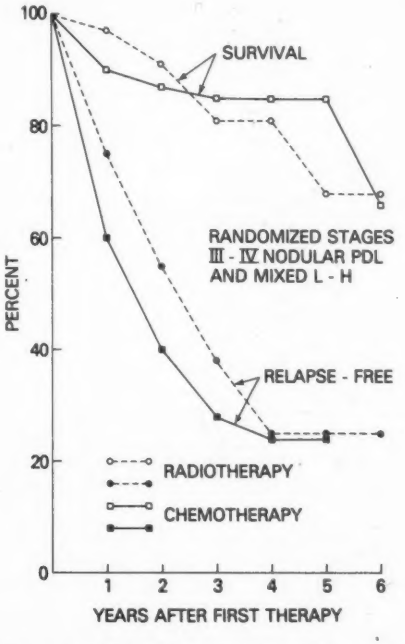

FIGURE 1.—% survival and relapse-free survival of patients with stage III and IV NPDL and nodular mixed lymphomas treated with combination chemotherapy or "systemic" radiotherapy.

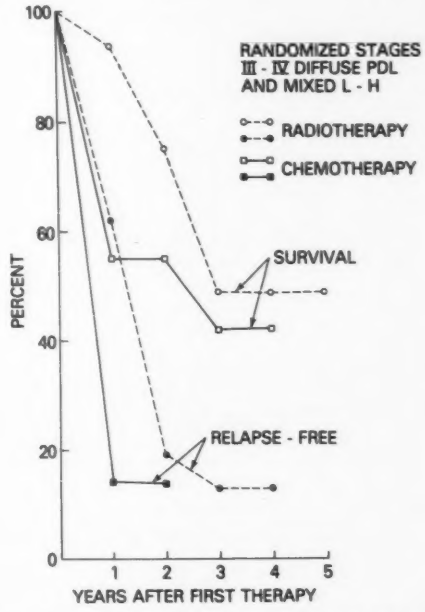

FIGURE 2.—% survival and relapse-free survival of patients with stage III and IV DPDL lymphomas treated with combination chemotherapy or "systemic" radiotherapy.

TABLE 3.—Response to initial therapy by histology

	Chemotherapy				Radiotherapy			
	Total No. of patients	CR*	PR	No response	Total No. of patients	CR	PR	No response
Nodular	42	26 (62%)	12	4	33	28	4	1
NPDL	29	19 (66%)	8	2	25	22	3	—
Nodular mixed	13	7 (54%)	4	2	8	6	1	1
Total		38/42 (90%)				32/33 (97%)		
Diffuse (DPDL)	8	1 (13%)	4	3	16	11	1	4
Total		5/8 (63%)				12/16 (75%)		
Overall totals (CR + PR)		43/50 (86%)				44/49 (90%)		

**See* text for the differences in restaging techniques in the 2 groups.

persistent liver involvement following completion of treatment was not undertaken in the group receiving radiotherapy. Although all other restaging procedures were identical in the two groups, it is likely that repeat liver biopsy would have detected persistent microscopic disease in some of the 25 radiotherapy patients who had hepatic involvement before therapy.

A summary of the types of treatment for all patients in the trial according to histologic subtype is shown in table 2.

RESULTS

Response to Initial Radiotherapy

Forty-four of the 49 patients treated with radiotherapy (90%) had a CR or PR after initial therapy. Thirty-nine of these (80%) had complete disappearance of all evidence of disease. However, 19 of the patients achieving CR (49%) had initial liver involvement which was not reassessed. Five patients (10%) had no significant tumoricidal effect. CRs were noted with all three radiotherapy techniques used. The response to therapy is shown in table 3.

Twenty-eight of the 33 patients with nodular histology (85%) achieved a CR compared to 11 of 16 patients (69%) with diffuse histology. The difference is not statistically significant, but seven (44%) of the patients with diffuse histology who achieved CR had pretreatment liver involvement which was not reassessed. Three of these patients had liver involvement as their only site of visceral disease. The duration of survival and the duration of relapse-free survival for the patients with nodular histology (fig 1) and diffuse histology (fig 2) are shown. The median survival for the entire group of advanced nodular lymphoma patients has not yet been reached but will exceed 5 years for patients treated with either modality. The median survival for those with diffuse histology has been reached and is 36 months for those treated with radiotherapy.

Relapse-free survival is less impressive. The median duration of relapse-free survival for those treated with radiotherapy is 26 months for the nodular group and 17 months for those patients with diffuse histology. At 4 years after initial therapy only 24% of the nodular histology patients and 13% of the diffuse histology patients remain in continuous unmaintained CR.

Patients relapsing after initial radiotherapy or those achieving a PR were re-treated with intermittent doses of TBI of 10–20 rads on a schedule individually monitored according to toxicity and disease control. Patients no longer responsive to such therapy (20) were given chemotherapy which in most instances was CVP or C–MOPP, depending upon histology. Twenty-six patients in the radiotherapy group (53%) eventually received subsequent chemotherapy.

Response to Initial Chemotherapy

Forty-three of the 51 patients treated with CVP or C–MOPP chemotherapy (86%) had a CR or PR. Twenty-seven (54%) achieved CR. Seven patients (14%) had no significant response to induction therapy. The response to therapy is shown in table 3. Twenty-six of the 42 patients with nodular histology (62%) achieved CR compared to one of eight with diffuse lymphoma (13%); the difference is significant ($P < 0.05$). Most patients achieved CR with six cycles of therapy but up to 12 cycles were sometimes required to achieve CR verified by restaging.

The duration of survival and the duration of disease-free survival are shown for patients with

nodular histology in figure 1 and diffuse histology in figure 2. The median survival for all patients with nodular histology treated with combination chemotherapy has not yet been reached but will exceed 5 years. The median survival for those patients with diffuse histology has been reached and is 30 months.

As with the patients treated with radiotherapy, the disease-free survival is not nearly as impressive. The median duration of relapse-free survival for those treated with chemotherapy is 22 months for the nodular group and 11 months for those with diffuse histology. At 4 years after initial chemotherapy, 24% of nodular and 13% of diffuse histology patients remain disease free, figures identical to those achieved with initial radiotherapy.

Patients relapsing after initial chemotherapy were usually reinduced with the same regimen. Relapse of disease has occurred in 16 of the 27 patients with CR (59%). Relapse of disease could be successfully re-treated by repeat courses of CVP or C–MOPP in ten of these patients (63%). Patients achieving a PR to initial therapy were treated with intermittent cycles of combination chemotherapy but in no instance did > 12 cycles achieve a CR.

Toxicity Associated With Induction Therapies

The major forms of acute toxicity associated with radiotherapy were hematologic and hepatic. Radiation-induced hepatitis developed in three patients who received whole-abdominal irradiation. Reversible bone marrow depression was observed routinely in patients treated with radiotherapy. Hematologic toxicity was more apt to manifest as thrombocytopenia than leukopenia in patients receiving radiotherapy. Mean nadir platelet counts 1 month after completion of therapy were 70,000 ± 60,000/mm^3. Seventeen patients had nadir platelet counts of ≤ 50,000/mm^3. Blood count suppression persisted beyond 2 months in 12 patients, and one patient had persistent thrombocytopenia for > 2 years.

In contrast to thrombocytopenia, leukopenia was less frequently a significant problem. Mean nadir wbc counts with radiotherapy were 3080 ± 1700/mm^3. Only a single patient was hospitalized for an infectious complication at the nadir of radiation-induced leukopenia.

Late complications from radiotherapy can only be partially evaluated at this point in the trial. Three patients have developed acute or subacute myelogenous leukemia occurring 25–55 months after initial radiotherapy. All of these became manifest after further treatment with TBI and chemotherapy; two had received TNI in addition to their TBI.

Myelosuppression was also the primary dose-limiting toxicity for those patients receiving chemotherapy. In contrast to those treated with radiotherapy, leukopenia was more common and more severe than thrombocytopenia. Median nadir platelet counts were only 148,000 ± 74,000/mm^3 for those receiving chemotherapy, but median nadir wbc counts were 1250 ± 626/mm^3. Median nadir wbc counts were determined from the lowest nadir achieved during any of the therapeutic cycles. As a consequence of the leukopenia, more patients were hospitalized for suspected infections at the time of nadir leukopenia than for the radiotherapy group. Eighteen patients were hospitalized at some point during therapy. Nine of the entire group of chemotherapy patients (17%) had a documented infection and one patient died of disseminated candidiasis at nadir leukopenia during her first course of therapy.

Other acute toxicities were seen. Three patients developed hemorrhagic cystitis associated with cyclophosphamide therapy. Neurotoxicity commonly required dose reduction, especially late in the course of therapy. Three patients experienced neurotoxicity severe enough to require bed confinement.

No late complications have thus far developed in the group of patients receiving chemotherapy and no cases of myelogenous leukemia have occurred.

SECOND PROSPECTIVE TRIAL

The acquisition of patients for the first randomized trial was completed in September 1974. Several observations made during the first trial contributed to the design of the second. First, although both regimens had been responsible for an excellent overall survival rate (median survival > 5 years) in neither program had these been disease-free survivals in the majority of patients. Second, the toxicities appeared slightly discordant; that is, more severe leukopenia was associated with combination chemotherapy and more thrombocytopenia was associated with radiotherapy. Third, there appeared to be small but potentially significant differences in response by histologies; ie, more diffuse lymphoma patients achieved CR with radiotherapy and more nodular mixed lymphoma patients failed to relapse after CR with chemotherapy. Finally, of the 26 patients in the radiotherapy group who eventually failed this therapy and were treated with combination chemotherapy, 21 (81%) had responded and 12 of 26 (49%) achieved CRs. Despite the unfavorable bias of aggressive disease and extensive prior treatment, the combination chemotherapy regimens were tolerated relatively well. For these reasons, the second trial begun in September 1974 compares combination chemotherapy alone (CVP or C–MOPP) with TBI and chemotherapy (CVP or C–MOPP).

TABLE 4.—Patient characteristics
(chemotherapy vs TBI and chemotherapy)

	Chemotherapy	TBI and chemotherapy
No. of patients/No. of completed inductions	16/12	18/14
Mean age (range)	53 (39–67)	52 (22–67)
Sex (M/F)	10/6	10/8
Histology		
NPDL	7	8
Nodular mixed lymphoma	6	4
DPDL	3	4
Nodular histiocytic lymphoma	—	2
Stage		
II	2	2
III	7	5
IV	7	11

The chemotherapy is administered in a manner identical with the first trial. The TBI and chemotherapy is given as follows: 10-rad TBI is administered for 5 days the first week followed by five 10-rad courses the second week (total dose 100 rads). Chemotherapy is delayed until the wbc count is $\geq 4000/mm^3$ and the platelet count is $\geq 100{,}000/mm^3$ (usually 4–6 weeks after TBI). Patients with DPDL and NPDL subsequently receive CVP and those with nodular mixed or nodular histiocytic receive C–MOPP. Sliding-scale modifications of chemotherapy are made in the manner identical with the chemotherapy-alone arm of the trial.

Thus far, 34 patients have been randomized; 18 have received TBI and chemotherapy and 16 have received chemotherapy alone. The characteristics of the patient groups are shown in table 4. With a median followup of only 14 months, it is impossible to accurately assess the relative success of either regimen. Preliminary response to therapy thus far is shown in table 5. All patients have responded to therapy. CRs have been achieved in eight of 12 evaluable chemotherapy patients (67%) and nine of 14 TBI and chemotherapy patients (64%).

Relapses thus far have occurred in four of eight patients receiving chemotherapy after 7, 8, 13, and 15 months of unmaintained remission. Three of the nine CR patients receiving TBI and chemotherapy have relapsed at 6, 6, and 9 months.

Figure 3 indicates the overall and disease-free survival at this point in the trial. No patient in either arm of the trial has died (maximal followup of 2 years). Disease-free survival appears similar for the two groups thus far.

DISCUSSION

The initial trial was designed to compare the effectiveness of two forms of systemic therapy for advanced lymphoma. It is apparent that high overall response rates may be achieved with either approach (90% for radiotherapy; 86% for chemotherapy) and that CRs are relatively common (60%–80%). Differences in posttherapy restaging techniques make precise comparisons of CR rates difficult. In spite of the relatively intensive therapy administered to patients with either modality and the relatively high CR rate, the majority of patients relapse over the first 42 months of followup. In spite of the high relapse rate patients tend to retain their responsiveness to therapy and long survivals are the rule in these good prognostic histologies, even with advanced disease. Overall median survival of all patients in this trial will exceed 5 years regardless of initial therapy used. However, disease-free survival is not common. Relapse-free survival rates at 4 years' followup in this study, regardless of induction regimen, are 13% for the diffuse and 24% for the nodular lymphomas. The failure of most patients to experience durable, unmaintained remissions and the requirement for intermittent, if not continuous, treatment is unsatisfactory. The early survival curve for nodular lymphomas in this series does not differ from that of the Stanford series using sequential single agents and/or high-dose nodal irradiation (4). Whether these more intensive approaches will render a small fraction of patients

TABLE 5.—Response to therapy
(chemotherapy vs TBI and chemotherapy)

	Chemotherapy			TBI and chemotherapy		
Histology	CR	PR	No response	CR	PR	No response
Nodular	7	2	0	8	1	0
Diffuse	1	2	0	1	4	0
Totals	8 (67%)	4 (33%)		9 (64%)	5 (36%)	

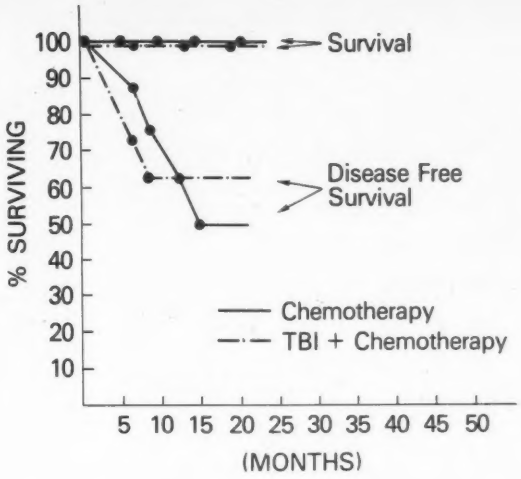

FIGURE 3.—Survival in non-Hodgkin's lymphoma with chemotherapy vs TBI and chemotherapy.

free of disease at 10-year followup remains to be seen.

The second prospective trial attempts to use both TBI and chemotherapy in an amalgamated approach. Initial experience with the combined approach indicates that it can be given safely without augmenting the toxicity of either modality alone as long as hematologic recovery is allowed to occur between the two therapies. Followup is too short for meaningful conclusions, but thus far the initial response rates are similar to either modality alone.

LIST OF COMPOUNDS

C-MOPP = cyclophosphamide, Oncovin (vincristine), prednisone, and procarbazine

CVP = cyclophosphamide, vincristine, and prednisone

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate

Prednisone: NSC-10023; CAS reg. No. 53-03-2; pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-

Procarbazine: NSC-77213; CAS reg. No. 491-88-3; *p*-toluamide, *N*-isopropyl-α-(2-methylhydrazino)-, monohydrochloride

Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1)

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Management of Childhood Non-Hodgkin's Lymphoma[1]

Sharon B. Murphy[2,3,*]

SUMMARY

Treatment of children with non-Hodgkin's lymphoma (NHL) should be determined by the primary anatomic location and extent of disease. Abdominal NHL, when localized to the gastrointestinal tract and completely resected, is curable in 80% of cases when surgery is followed by whole abdominal radiotherapy (2000–2500 rads) and combination drug therapy. Optimal management for children with advanced abdominal tumors is not established, though combination chemotherapy with cyclophosphamide, vincristine, and methotrexate or cyclophosphamide, vincristine, methotrexate, and prednisone in American Burkitt's patients with abdominal tumors results in a complete response frequency of 96% and a 2-year calculated survival rate of 41%. Mediastinal NHL should be treated with an intensive antileukemia regimen. Adequate local irradiation plus a Total Therapy drug regimen for 2–3 years resulted in cure of eight of ten children with NHL localized to the head and neck. Prophylactic central nervous system (CNS) treatment should not be given to all children since the risk of CNS disease as the site of first relapse is remote in certain subgroups of patients. Controlled trials are necessary to establish the efficacy of CNS prophylaxis in patients at high risk of CNS disease. Current intensive multiple-drug regimens using high-dose cyclophosphamide, moderate- to high-dose methotrexate, adriamycin, vincristine, prednisone, and other agents combined with radiotherapy are resulting in improved overall survival compared to previous experience.

[Cancer Treat Rep 61:1161–1173, 1977]

Application of an intensive combined modality approach employing radiation and multiple-drug chemotherapy for the management of childhood lymphomas has clearly resulted in improved survival in recent years. However, significant problems in the management of these disorders in children remain and require better solutions. Simple translation to children of approaches useful in the management of adults with non-Hodgkin's lymphoma (NHL) is inappropriate because of marked differences in tumor histologic composition, anatomic sites of involvement, predilection for evolution to acute leukemia, and sensitivity to drug therapy. Furthermore, there is an appropriately greater concern over the risk in children of both immediate and long-term adverse effects of intensive combined modality therapy, particularly in those children with favorable localized presentations who may be cured with less toxic regimens.

Treatment for lymphomas has traditionally depended on stage of disease. While the Ann Arbor staging system is applicable to children with NHL and has been shown to have prognostic significance (1–3), it is not particularly well suited. The rarity of stage III disease in children is notable (1,3–5), and mediastinal NHL, even though confined to a single anatomic site, has a poor prognosis. An acceptable

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Stage I
Single tumor (extranodal) or single anatomic area (nodal), with the exclusion of mediastinum or abdomen.

Stage II
Single tumor (extranodal) with regional node involvement.
Two or more nodal areas on the same side of the diaphragm.
Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm.
Primary gastrointestinal tract tumor, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only.

Stage III
Two single tumors (extranodal) on opposite sides of the diaphragm.
Two or more nodal areas above and below the diaphragm.
All primary intrathoracic tumors (mediastinal, pleural, thymic).
All extensive primary intra-abdominal disease.

Stage IV
Any of the above with initial CNS and/or bone marrow involvement.

FIGURE 1.—NHL-75 staging system.

staging classification and minimum requisite staging procedures for childhood NHL need to be further defined. In the meantime, alternate schemes for staging have been proposed (*see* fig 1 and refs 6 and 7, for example).

It is also necessary to agree on the distinction between NHL with bone marrow involvement and acute leukemia with bulky extramedullary disease at diagnosis. In some cases the distinction is arbitrary, the cutoff usually being ≤25% tumor cells in initial marrow cell differentials. Diffuse marrow replacement or circulating blast cells at diagnosis conventionally defines "leukemia," and treatment should then be the same as for acute leukemia, lymphoblastic or non-lymphoblastic. Current lack of uniformity in defining leukemia versus stage IV NHL due to marrow involvement makes interpretation of results of therapy extremely difficult, since end results for both NHL and acute leukemia trials are improved if substantial numbers of children who would conventionally be considered "leukemic" are treated under the NHL protocols.

The prognostic value of the Rappaport classification is not clearly established in children (1–4). Since roughly 95% of all the lymphomas occurring in children are of the diffuse type (1), distinguishing the rare children presenting with nodular NHL is largely an academic exercise. Introduction of extensive new functional immunologic studies has already created a fragmented approach to therapy. For example, the convoluted T-lymphocytic variety of NHL so common in adolescent boys receives the same intensive therapy as is used for so-called high-risk acute lymphoblastic leukemia (ALL) in some centers, whether or not the patient is leukemic at the time of diagnosis. The marked functional heterogeneity of immunologic markers already described for childhood lymphomas (5) makes it prudent to await the outcome of further prospective studies in large numbers of children before accepting the suggested clinical correlations as a valid guide to therapy.

Owing to the lack of uniformity in staging and the unsettled state of classification, the optimal therapy for children with NHL will be discussed in this review according to the dominant anatomic site of presentation. Most children with NHL have abdominal, mediastinal, or head-neck primaries, and these sites will be discussed separately. Current management of Burkitt's lymphoma (BL) will also be reviewed. While the occurrence of BL (strictly defined) in American children is rare (1,8), its clinical presentation overlaps to an extent other abdominal or generalized presentations of diffuse undifferentiated NHL in children, and principles of treatment are similar. The issue of prophylactic treatment of the central nervous system (CNS) will be addressed. The SJCRH experience in the management of NHL and its current approach will be compared to published results and ongoing trials.

Abdominal NHL

The abdomen is the most common site of origin of NHL in children, accounting for 30%–40% of reported series (4). In Jenkin's series of 102 children (6), 22% had primary involvement of the gastrointestinal tract and 18% had extensive intra-abdominal disease of uncertain origin, the latter commonly associated with ascites and massive unresectable retroperitoneal, mesenteric, and/or pelvic tumor. Of the bowel primaries, the terminal ileum, cecum, appendix, and ascending colon are the predominant anatomic sites involved in children. The comparative rarity of leukemic change or meningeal involvement in abdominal NHL is notable (9,10), especially as the site of first relapse.

Optimal therapy for children with abdominal NHL consists of a combination of surgery, radiation, and multiple drugs. The prognosis is excellent for children with localized intestinal disease who are treated with grossly complete surgical resection followed by whole abdominal irradiation—2500–3000 rads in 4 weeks. Approximately 70%–80% of these children are cured (10,11). The prognosis for children with advanced, unresectable abdominal disease is far less optimistic, that situation being nearly universally fatal within 6 months despite irradiation and chemotherapy (1,6,11). The importance of complete surgical excision is underscored by the recently published experience from Memorial Sloan-Kettering concerning 31 cases of abdominal NHL (12). All but one of the seven survivors had complete excision of tumor before chemotherapy or irradiation. Where incomplete excision or bi-

opsy only was carried out, only one patient survived despite aggressive chemotherapy and irradiation. In a series of African patients with abdominal presentations of BL treated with surgery and chemotherapy, the addition of surgical bulk reduction produced highly significant differences in remission duration and survival reported by Magrath and co-workers (13) between patients with almost complete surgical resection of tumor (> 90%) and those who had partial resection or biopsy only.

Therefore, in children with abdominal lymphomas, surgical eradication of all gross tumor appears crucial to ensure the success of a subsequent program of irradiation and multiple drugs. Awareness of this has led some workers to recommend a "second-look" surgical procedure for resection of residual disease 3 weeks after initiation of chemotherapy in children in whom complete resection of tumor was not possible at the time of first laparotomy (12,14). If non-resectable disease were still present, residual tumor would be clipped and locally irradiated. If no tumor were found or all disease could be resected, no irradiation would be given. This pilot approach, which requires confirmation before it can be widely recommended, would surely have the effect of drastically reducing the use of whole abdominal irradiation. While this may improve tolerance to chemotherapy, the high frequency of intestinal and mesenteric node involvement observed with abdominal NHL makes the use of a whole abdominal radiation technique (15) a rational approach. Furthermore, the results of localized abdominal irradiation for gastrointestinal NHL are inferior to those of whole abdominal irradiation (10,11). And in the series of Nelson et al, 61% (11 of 18) of children with localized resectable intestinal NHL who received surgery and chemotherapy only manifested local recurrences (10).

Treatment for extensive unresectable abdominal NHL therefore remains difficult, and the relative roles of surgery, radiation, and chemotherapy require further definition.

Burkitt's Lymphoma

BL is a type of diffuse undifferentiated NHL characterized by rapid onset and rapid progression of multifocal disseminated disease involving abdominal and/or pelvic viscera, retroperitoneal soft tissues, multiple quadrants of the jaw, kidney, liver, gonads, endocrine organs, and CNS (16). BL is predominantly a tumor of childhood, though it may also occur in young adults. The median age for 30 American patients reported from the NCI was 11 years, with a range from 2 to 27 years (17). Response to treatment, risk of relapse, and mortality are related to the initial site(s) and volume of tumor (7,17).[1] Consequently, a clinical staging system has been devised (7). Patients with minimal tumor burden (ie, stages A or B, single or multiple extra-abominal sites, or stage AR, abdominal disease > 90% resected) have a better prognosis than stages C or D (ie, gross intra-abdominal tumor, with or without extra-abdominal, CNS, or bone marrow involvement).

The efficacy of chemotherapy in BL is well recognized. In an analysis of chemotherapy response in African patients with BL, Ziegler reported that 95 of 101 evaluable patients achieved a complete remission (CR) in virtually all cases following a single dose of cyclophosphamide, 40 mg/kg iv (18). BL is potentially curable with chemotherapy alone, though the relapse rate in African patients with large generalized tumors is high (61%) following single or multiple doses of cyclophosphamide or combination therapy with cycles of cyclophosphamide, vincristine, methotrexate, and cytosine arabinoside (18). In a recent analysis of 54 evaluable patients treated according to two sequential NCI treatment protocols[1] (COM or COMP; *see* table 1), Ziegler reported an overall CR frequency of 96% in 50 evaluable patients. Calculated actuarial 2-year survival for 17 stage A, B, and AR patients was 88%, compared to 41% for 37 stage C and D patients.[1] No difference in survival between protocol treatments was apparent. Remissions in these patients were largely unmaintained. The overall relapse rate was 44%.

Initially, BL tumor cells are markedly sensitive to chemotherapy, perhaps as a consequence of their high proliferative and cellular turnover rates (19). Acute metabolic complications attributable to massive lysis of tumor within 24–48 hours of initial therapy include azotemia, hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and lactic acidosis (17). Renal shutdown and even sudden death may ensue. Intensive monitoring and facilities for dialysis must be available before undertaking therapy in patients with an initial large tumor burden.

Mediastinal NHL

Mediastinal NHL is a distinct clinical entity limited almost exclusively to adolescent boys and characterized by an aggressive clinical course, evolution to acute leukemia in up to 90% of cases, and a high

[1]Ziegler JL. Treatment results of 54 American patients with Burkitt's lymphoma are similar to the African experience. N Engl J Med 297:75–80, 1977.

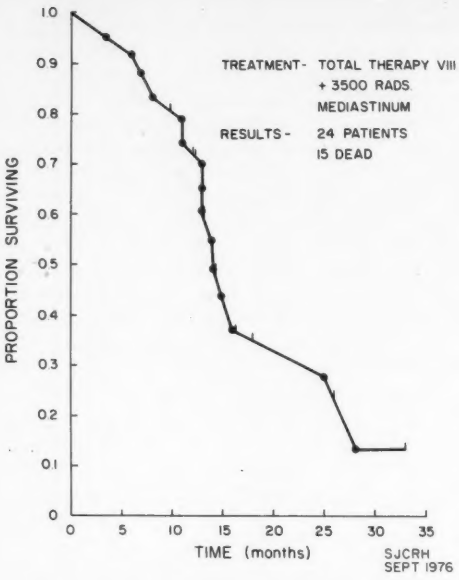

FIGURE 2.—Actuarial survival of 24 children with mediastinal NHL, leukemic at the time of diagnosis, calculated by the Kaplan-Meier procedure. Patients were treated with a Total Therapy VIII regimen, including mediastinal irradiation and CNS prophylaxis; 10 of 24 patients are surviving 10–33+ mos from diagnosis.

incidence of CNS spread (6,9,20,21). The resemblance of mediastinal NHL to acute leukemia associated with a mediastinal mass in childhood is striking, in terms of both clinical features and response to therapy. Blast cells with the capacity to form spontaneous rosettes with sheep erythrocytes have also been demonstrated in both conditions (22,23), suggesting a common origin from thymus-derived cells. Possibly the only difference between mediastinal NHL without initial bone marrow involvement and acute leukemia with a mediastinal mass is the timing of the diagnosis.

Treatment of mediastinal NHL with either an antilymphoma-like or an intensive antileukemia-like regimen has generally not been successful. Ten of the 11 children (91%) with mediastinal NHL reported from the M. D. Anderson Hospital experience developed bone marrow involvement, and there were no long-term survivors, following treatment with radiotherapy plus one or more drugs (9). Before introduction of the LSA-L_2 protocol, Wollner et al reported no 2-year survivors among ten children with mediastinal primaries (4). At Stanford University Hospital from 1961 to 1971, children with mediastinal NHLs were carefully staged and managed primarily with high-dose radiotherapy to involved or extended fields in an attempt to eradicate all known disease (2). With this approach, nine of 11 patients with mediastinal involvement manifested bone marrow involvement. Jenkin reported achieving an initial CR rate of 86% in 21 evaluable children with mediastinal NHL using radiation (2000 rads to the thorax, neck, and axilla), prednisone, vincristine, and/or 6-mercaptopurine as initial agents (6). The overall disease-free survival at 2 years, however, was < 10%.

At SJCRH, the early experience with treatment of mediastinal NHL without initial marrow involvement with an antileukemia Total Therapy approach plus irradiation to the mediastinum (24) suggested that, in some cases, leukemic conversion may be prevented by continuing combination drug therapy. One child from the original reported series is, in fact, surviving without treatment and has been in remission for > 8 years. Another child in the originally reported series died 40 months from diagnosis after suffering a CNS relapse while not receiving therapy, with subsequent leukemic conversion. However, the remaining four of the total six children with mediastinal NHL who have been treated by that approach died from interstitial pneumonia while in CR.[5]

The recent results obtained at SJCRH in the treatment of children with mediastinal tumors who were leukemic at diagnosis are shown in figure 2.[5] All children were treated according to Total Therapy VIII, a protocol which used vincristine, prednisone, and L-asparaginase for induction, with the addition of 3500 rads of cobalt 60 irradiation to the mediastinum. This was followed by prophylactic treatment of the CNS with cranial irradiation (2400 rads) plus intrathecal methotrexate (12 mg/m² × five doses). Maintenance therapy with daily 6-mercaptopurine and weekly methotrexate and cyclophosphamide was then continued for 2–3 years. Twenty-three of 24 children (96%) achieved a CR. Nine patients are still surviving from 10 to 33+ months from diagnosis. Only one child has been removed from therapy and is in continuous CR. This experience compares very unfavorably with our general experience with childhood ALL (25).

Wollner et al have recently reported excellent results in nine children with primary mediastinal NHL treated according to the multiple-drug LSA-L_2 protocol (4) (*see* table 1 and fig 3). Only one of nine patients received radiotherapy in addition to drugs during induction. Actuarial survival was

[5]Aur RJA. Personal communication.

TABLE 1.—Current therapy for childhood NHL

Source	Regimen	
Murphy, SJCRH	NHL-75	Induction (4–6 wks): Stages I and II: Vincristine, 1.5 mg/m² iv on Days 0, 7, 14, 21, 28, 35 Cyclophosphamide, 1200 mg/m² iv on Days 0, 21, 42 Prednisone, 40 mg/m² orally daily for 4 wks Involved field radiotherapy (3500–4000 rads) Stages III–IV: Vincristine, cyclophosphamide, and prednisone (as above) Adriamycin, 45 mg/m² iv on Days 0, 21, 42 Randomization for radiotherapy, as above, or none CNS prophylaxis (2–3 wks): Stage I: None Stages II–IV: Randomization for— Cranial irradiation (2400 rads) + methotrexate, 12 mg/m² intrathecally × 5 doses, or none Maintenance (18 months): 6-Mercaptopurine, 75 mg/m² orally daily Methotrexate, 30 mg/m² orally weekly
Wollner et al (ref 4), Memorial Sloan-Kettering Cancer Center	LSA_2-L_2	Induction: Cyclophosphamide, 1200 mg/m² iv on Day 1 Vincristine, 1.5–2.25 mg/m² iv on Days 3, 10, 17, 24 Prednisone, 60 mg/m² orally daily on Days 3–31 Daunorubicin, 60 mg/m² iv on Days 12, 13 Methotrexate, 6.25 mg intrathecally on Days 5, 27, 30 ± Radiation therapy to single or multiple bulky disease areas Consolidation: Cytosine arabinoside, 150 mg/m² iv daily × 15 doses 6-Thioguanine, 75 mg/m² orally daily × 15 doses, then L-Asparaginase, 6000 units/m² iv × 12 doses, then Methotrexate, 6.25 mg intrathecally × 2 doses, then BCNU, 60 mg/m² iv once Maintenance (repetitive 5-day cycles with 7–10-day intervals): 6-Thioguanine, 300 mg/m² orally × 4 + cyclophosphamide, 600 mg/m² iv × 1 Hydroxyurea, 2400 mg/m² orally × 4 + daunorubicin, 45 mg/m² iv × 1 Methotrexate, 10 mg/m² orally × 4 + BCNU, 60 mg/m² iv × 1 Cytosine arabinoside, 150 mg/m² iv × 4 + vincristine, 1.5 mg/m² iv × 1 then methotrexate, 6.25 mg intrathecally × 2
Jenkin (study chairman), CCSG (*see* footnote 9)	Protocol CCSG-551 (COMP)	LSA_2-L_2 treatment regimen vs Cyclophosphamide, 1.2 g iv on Day 1 Vincristine, 2.0 mg/m² iv on Days 3, 10, 17, 24 Methotrexate, 300 mg/m² iv on Day 12 Methotrexate, 6.25 mg/m² intrathecally on Days 5, 31, 34 Prednisone, 60 mg/m² orally daily for 1 mo + radiotherapy to all sites grossly involved at diagnosis Maintenance consists of drug cycles, COMP + intrathecal methotrexate essentially as above, repeated monthly

TABLE 1.—Current therapy for childhood NHL—Continued

Source	Regimen	
Freeman and Tefft (study chairmen), ALGB (*see* ref 33 and footnote 10)	ALGB-7542	Induction: Vincristine, 2 mg/m² iv on Days 1, 8, 15, 22 Dexamethasone, 6 mg/m² orally daily for 4 wks Methotrexate, 12 mg/m² intrathecally on Days 1, 8, 15, 22 Radiation therapy (3500–4000 rads), begin Day 15 Stage IV patients are randomized for an additional intensification, consisting of: Vincristine, 2 mg/m² iv on Days 36, 57, 78 Dexamethasone, 6 mg/m² orally daily for 1 wk on Days 57, 78 Methotrexate, 12 mg/m² intrathecally on Days 36, 57, 78 Methotrexate, 500 mg/m² iv over 24-hr drip on Days 36, 57, 78 Citrovorum factor, 12 mg/m² iv or im 24 hrs after iv methotrexate Maintenance patients are randomized to either/or (*a*) Antileukemia-like: Methotrexate, 15 mg/m² orally weekly 6-Mercaptopurine, 75 mg/m² orally daily Cyclophosphamide, 500 mg/m² iv × 1 Vincristine, 2 mg/m² iv × 1 Dexamethasone, 6 mg/m² orally daily × 1 wk } × 1 monthly (*b*) Antilymphoma-like (monthly pulses): Cyclophosphamide, 1 g/m² iv × 1 Vincristine, 2 mg/m² iv × 1 Dexamethasone, 6 mg/m² orally daily × 1 wk
Jaffe, Sidney Farber Cancer Center	APO	Ref 38
Ziegler, NCI (*see* footnote 4)	Protocol 74-1 (COM)	Cyclophosphamide, 1000 mg/m² iv on Day 1 Vincristine, 1.4 mg/m² iv on Day 1 Methotrexate, 15 mg/m² intrathecally on Days 1, 4 Methotrexate, 15 mg/m² iv on Days 2, 3 (repeated at 2-wk intervals for 3 courses; 2 wks after 3rd course, stage AR, C, D patients receive whole abdominal irradiation, 2100 rads in 18 elapsed days)
	Protocol 75-6 (COMP)	Induction: Cyclophosphamide, 1000 mg/m² iv on Day 1 Vincristine, 1.4 mg/m² iv on Day 1 Methotrexate, 12.5 mg/m² iv on Days 1, 3, 4 Methotrexate, 12.5 mg/m² intrathecally on Days 2, 5 Prednisone, 1000 mg/m² iv on Days 1–5; (repeat cycle on Day 15) Consolidation on Day 29: Cyclophosphamide, 1200 mg/m² iv × 2 doses, 24 hrs apart Methotrexate, 12.5 mg/m² intrathecally with citrovorum factor rescue, then radiotherapy as above for patients in CR—stage AR, C, D

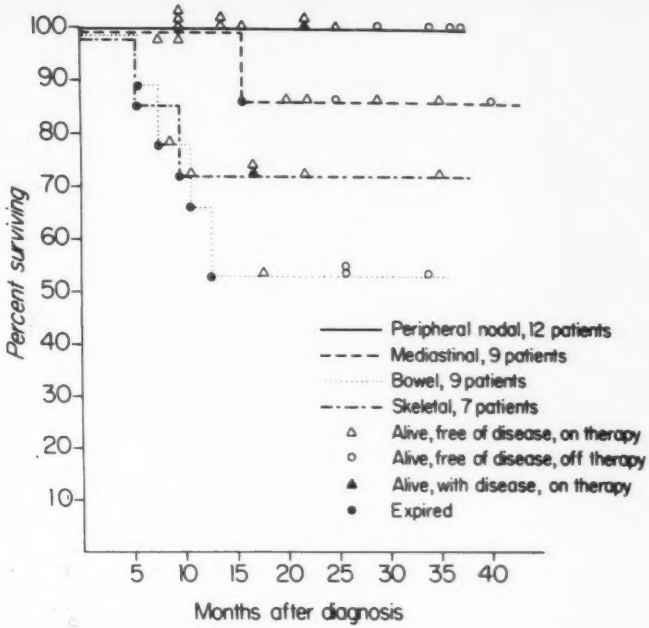

FIGURE 3.—Actuarial survival according to primary site of involvement (peripheral nodal, mediastinal, skeletal, and bowel) for children with NHL treated according to the LSA-L_2 protocol of Wollner et al (reproduced *from* Med Pediatr Oncol 1:259, 1975).

reported to be 88% 3–4 years after diagnosis, with half the patients no longer receiving therapy (4).

Mediastinal NHL thus should be treated with an intensive multiple-drug antileukemia-like regimen. While published series are uncontrolled, they do not suggest that radiation therapy to the mediastinum is necessary or exerts a positive influence on survival. In fact, the hazard of immunosuppression created by the combined use of multiple-drug therapy plus mediastinal irradiation approaches a level of toxicity which may be considered unacceptable. In our experience the incidence of *Pneumocystis carinii* pneumonitis is directly related to the intensity of immunosuppressive therapy (26). Nine of 15 children (60%) with mediastinal NHL who were leukemic at diagnosis and were treated as described above developed *P. carinii* pneumonia, proved by pulmonary aspiration.[6] Double-blind, placebo-controlled studies, in progress at our institution since October 1974, suggest that the prophylactic daily oral administration of trimethoprimsulfamethoxazole is extremely effective in reducing the occurrence of *P. carinii* in our patients at high risk for this infection (27).[6] In the future, incorporation of such prophylactic treatment into combined modality regimens for patients with mediastinal NHL promises a significant reduction in morbidity and mortality related to *P. carinii*.

[6]Hughes WT. Personal communication.

Head-Neck NHL

NHL localized to the head and neck has a comparatively better prognosis than disease of other primary sites in children. Traggis and colleagues reported a 51.7% survival rate in 34 children, categorized retrospectively as stage I or II according to the Ann Arbor system, and treated with differing combinations of surgery, radiotherapy, and/or single- or multiple-agent chemotherapy (28). Aur and co-workers have treated ten children with NHL localized to Waldeyer's ring and/or unilateral or bilateral cervical nodes with a Total Therapy regimen plus involved field irradiation (24), and eight of ten are surviving for 17–99+ months (*see* footnote 5). This relatively favorable experience has not been universal, however, as Jenkin reported no survivors among 11 children with extranodal head-neck primaries treated primarily with adequate wide-field irradiation (6). It would appear, therefore,

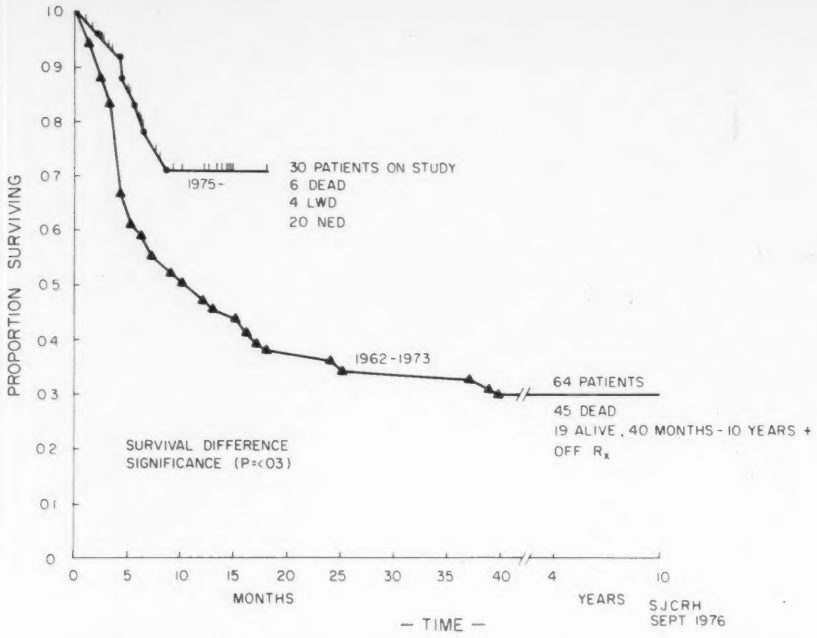

FIGURE 4.—Actuarial survival of 30 children, treated according to NHL-75 (*see* text) in comparison to previous SJCRH experience in treatment of NHL in 64 children from 1962 to 1973. Survival difference is significant ($P < 0.03$, generalized Wilcoxon test).

that aggressive chemotherapy must be combined with adequate local irradiation to ensure optimum survival for children with head-neck NHL.

Prophylactic Treatment of the CNS

Lymphomatous involvement of the CNS is uncommon at diagnosis in children with NHL, but increases in incidence with progressive disease. The overall incidence in reported childhood series is approximately 30% (1,6,9). An even higher incidence of CNS involvement is reported for mediastinal primaries (9,21) and for BL (29,30). Long-term survival or cure after CNS disease ensues is generally not observed (1,21,31,32). Therefore, attempts at prophylaxis appear warranted, particularly since improved systemic treatment and longer survival are likely to increase the relative importance of CNS disease as a cause of treatment failure. Both the rationale and approach taken to prophylaxis have been analogous to those taken in preventing CNS leukemia in childhood ALL, namely cranial and/or neuroaxis irradiation and/or intrathecal therapy with methotrexate or cytosine arabinoside or both. The same measures are useful for treatment of established CNS disease.

However, certain groups of children appear at low risk of developing CNS disease as the site of first relapse, and the proven and potential risks of prophylactic therapy appear to outweigh possible benefits. Patients with localized favorable stage I presentations have a $< 10\%$ risk of developing a first relapse in the CNS.[7] No child with disease localized to the gastrointestinal tract and resected developed CNS disease in two recent series (10,21). Furthermore, CNS involvement in childhood NHL typically appears in the setting of progressive disease, usually after bone marrow relapse (9). In the experience reported from Stanford and from Roswell Park, no patient had CNS relapse as the initial site of failure, without other evidence of disseminated neoplasm (2,33). Similarly, in Ziegler's series of American BL patients, relapse in the CNS as the sole manifestation of disease recurrence was not observed in any patient, but was invariably associated with systemic tumor relapse (*see* footnote 4).

[7] Murphy S. SJCRH unpublished results.

Preliminary trials of prophylaxis of CNS disease in NHL have not demonstrated convincing benefit in children. In the only randomized controlled trial reported to date, Ziegler and Bluming treated a total of ten patients with BL prophylactically with the combination of intrathecal methotrexate and cytosine arabinoside and compared these to a control group. Five of ten patients in the treatment group and four of ten in the control group subsequently developed malignant pleocytosis (30). In the SJCRH experience with mediastinal tumors, leukemic at diagnosis, five of 23 patients achieving remission developed CNS disease as their initial relapse on therapy, despite prophylaxis with cranial irradiation and intrathecal methotrexate (*see* footnote 5). Sullivan reports a similar experience with a small number of non-Burkitt's, convoluted cell-type cases. Active CNS disease developed in three of seven children given prophylaxis and in three of four not given CNS prophylaxis (34). Wollner and colleagues reported spread to CNS in seven of 43 (17.5%) patients treated with intermittent intrathecal methotrexate and the LSA-L_2 regimen (31,32).

Controlled trials are therefore needed to establish the efficacy of preventive CNS therapy in childhood NHL. Only patients at high risk of the complication, such as those with mediastinal primaries or generalized disease, should be so treated. Risks of therapy associated with administration of iv and intrathecal methotrexate and cranial irradiation, such as leukoencephalopathy (35,36), must be weighed against possible benefits. Until radiotherapy and chemotherapy achieve more effective and uniform control of systemic disease, preventive CNS therapy is likely to have little impact on survival.

SJCRH Experience

1962–1975

Pinkel and co-workers recently reviewed the experience with treatment of NHL in children at SJRCH from 1962 to 1973 (8) (*see* fig 4 and table 2). Treatment during that interval was not uniform, but consisted usually of single- or multiple-agent chemotherapy for all patients, or an antileukemia Total Therapy regimen, combined with radiotherapy (2500–4000 rads). Known tumor-bearing areas were irradiated in all stage I–II patients (Ann Arbor classification). Stage III–IV patients were not uniformly treated with irradiation. Nineteen of 64 patients (30%) are long-term survivors. Seventeen of the 19 (89%) had localized disease (stage I–II) at diagnosis.

From 1968 to 1975, Aur and colleagues treated a favorable subgroup of NHL patients uniformly with a Total Therapy drug regimen plus involved field radiotherapy (1600–3500 rads) (24). Twenty-five children were clinically staged and found to have disease localized to a single site or limited by the diaphragm to either the upper or lower half of the body, without involvement of marrow or spinal fluid. Eight of ten stage I patients were cured. Twelve patients from this series (48%) are surviving, 17–99+ months from diagnosis (table 2) (*see* footnote 5).

1975–Present

A new protocol for treatment of NHL was introduced in 1975 (NHL-75). The adjuvant effect of radiotherapy to bulky tumor in poor prognosis pa-

TABLE 2.—2-yr survival by stage in childhood NHL

Series*	Ref No.	Study period (yrs)	No. of patients	% of patients surviving with—				
				Localized disease		Generalized disease		
				Stage I	Stage II	Stage III	Stage IV	Overall
a	8	1962–1973	64	92	20	11	0	30
b	24†	1968–1975	25	80	26.6	—	—	48
c	2	1961–1971	32	55	38	33	0	31
d	3	1950–1971	172	58	24	8		27
e	1	1960–1970	31	50		7.7		32
f	20	pre-1967	51	11.5		0		8
g	6	1958–1971	102					19
h	21	1958–1973	26					35
i	4	1964–1971	43	40		3		11
		1971–present	43	100		70		76

*Series a–f used the Ann Arbor staging classification; g and h used no staging; and i used a unique staging classification (ref 4).
†*See* footnote 5.

tients during induction and the value of CNS prophylaxis are being examined in a prospective randomized fashion. The study remains open. A brief outline of the methods employed and preliminary results are given below.

All untreated patients, ≤18 years old, with biopsy-proven NHL of any histologic type or anatomic presentation are eligible, provided they are not in a leukemic phase of NHL at diagnosis. For purposes of this study, "leukemia" was arbitrarily defined as the presence of circulating blast cells or > 25% replacement of marrow with blast cells.

Patients are clinically staged on the basis of the usual procedures, including hemogram, bone marrow aspirate and percutaneous biopsy, roentgenograms of the chest, skeleton, and skull, iv pyelogram, lumbar puncture with cytocentrifuge examination of cerebrospinal fluid, and scans of liver-spleen, bone, and whole body (^{67}Ga). Patients with head-neck primaries have additional roentgenograms of the facial bones, mandible, and soft-tissue views of the nasopharynx. Upper and lower gastrointestinal series are performed in patients with abdominal disease. Bilateral lower extremity lymphangiography is performed in patients whose clinically apparent disease is supradiaphragmatic, but not in patients with mediastinal primaries or obviously disseminated disease. Staging laparotomy and splenectomy are not performed. On the basis of this pretreatment evaluation, a stage is assigned (fig 1).

Treatment is based on stage of disease and is outlined in table 1.

Thirty children have been entered on NHL-75 thus far. The stages and locations of their tumors are shown in table 3. It can be seen that the majority of patients have advanced stages and/or unfavorable abdominal or mediastinal presentations. The frequency of CR after induction is 90%. The three boys who failed to attain remission all had unresectable abdominal disease with ascites and pleural effusions at diagnosis, showed a transient response to therapy, and then developed progressive, drug-resistant disease. At present, 20 of the 30 children are living free of disease while receiving therapy, and six have died. Four are alive with disease and continue to receive therapy. The overall survival curve, calculated according to the Kaplan-Meier procedure, is shown in figure 4. Compared to our previous experience, the survival on NHL-75 is significantly different ($P < 0.03$, two-tailed, generalized Wilcoxon test).

Results of the randomization for radiotherapy during induction in stage III–IV patients and for CNS prophylaxis are too preliminary to permit conclusions.

Other Current Approaches

Memorial Sloan-Kettering Cancer Center, Wollner and Coworkers

Since 1971, treatment for children with NHL has consisted of the LSA-L_2 regimen shown in table 1 (4,12,31,32). The LSA-L_2 regimen is essentially identical to the L_2 regimen, developed at Memorial Sloan-Kettering for the treatment of ALL, with the addition of a single large dose of cyclophosphamide at the onset of therapy plus radiation treatment in selected patients to areas of bulky tumor.

The results reported to date are unparalleled. Forty-three patients (ten with localized and 33 with generalized disease) have been treated with the drug regimen; 24 also received radiation therapy (200–6200 rads). CR was achieved in 40 of the 43 (93%) patients by 1 month. The actuarial survival for the 43 patients is 76%, with a median observation time of 25+ months and with 17 patients not receiving therapy after 2–3 years. The actuarial survival according to the primary site of involvement is shown in figure 3.

These results are a marked improvement over anything previously reported (table 2). It is difficult, however, to compare this series with others reported in the literature, for a number of reasons. Almost half of the children were stage IV, on the basis of initial bone marrow involvement (32), and many of these would be considered leukemic using

TABLE 3.—NHL-75: stage and anatomic locations of primary sites

Site	Stage I	II	III	IV	Totals
Abdominal		1	8	2	11
Mediastinal			4	2	6
Head-neck	1	2	1	4	8
Peripheral nodes	3		1		4
Bone				1	1
Totals	4	3	14	9	30

conventional criteria. The survival of children with NHL subsequent to bone marrow transformation may be surprisingly good. For example, in a series of 30 children with undifferentiated lymphoma, non-Burkitt's type reported from the M. D. Anderson experience, the median survival was 47 weeks for ten children who had both meningeal and bone marrow involvement, compared to a median survival of only 14 weeks for nine children without bone marrow changes (9). The survival of children with acute leukemia treated according to the L_2 regimen appears similar to the survival of the stage IV LSA-L_2 patients (4,37). Further complicating comparison with other reported series of childhood NHL are the high percentages of primary tumor involvement reported in peripheral nodes and skeleton, even multiple bony sites. Nodal and skeletal primaries certainly occur in childhood NHL, but are relatively much less common in other reported series. Lastly, the frequency of nodular forms of NHL in the LSA-L_2 series (six of 43, 14%) is higher than in any other childhood series reported. The frequency of nodular lymphoma in children is estimated to be very low, constituting only five of 178 cases (2.8%) collected from the literature (1).

Current studies by the national cooperative groups treating children with cancer seek to determine if the excellent results achieved in the single-institution pilot series reported by Wollner and her co-workers can be achieved in other centers. The Southwest Oncology Group is conducting a single-arm study using the LSA-L_2 protocol. Analysis of results to date is incomplete; however, five of six children with BL given this treatment have failed.[8] The Children's Cancer Study Group (CCSG) is ready to launch a two-arm randomized study comparing the LSA-L_2 regimen to a more conventional COMP plus radiotherapy approach (*see* below and table 1).[9]

CCSG, Jenkin and Colleagues

The CCSG is conducting a two-arm study comparing COMP plus radiotherapy to the LSA-L_2 regimen. The COMP protocol consists of pulses of high-dose cyclophosphamide, moderate-dose methotrexate, vincristine, and prednisone for both the induction and maintenance phases (table 1). Chemotherapy continues for 18 months. Intrathecal methotrexate is used on both regimens as prophylaxis for CNS involvement. This study is just under way, and no results are yet available.

Acute Leukemia Group B (ALGB), Freeman, Tefft, and Colleagues

The ALGB has recently adopted a combined radiotherapy/chemotherapy regimen, based on encouraging results reported from Roswell Park Memorial Institute in their pilot series (33) (table 1).[10] Children with well-differentiated or nodular histology, reticulum cell sarcoma limited to bone, or completely resected gastrointestinal lesions are not eligible for the study. Laparotomies with splenectomies for surgical staging are strongly encouraged by these investigators, as an Ann Arbor staging system is used. All patients receive induction with vincristine, dexamethasone, intrathecal methotrexate, and radiotherapy. Radiation (3500 rads in 3–4 weeks) begins in the third week of induction and is directed to the site(s) of involvement. Following induction, half of the stage IV patients will be randomized for an intensification phase, incorporating three high-dose methotrexate infusions with citrovorum factor rescue. A randomization for all patients will compare the efficacy of two forms of maintenance therapy continued for 2 years from diagnosis. The leukemia-like maintenance consists of daily 6-mercaptopurine, weekly methotrexate, and monthly pulses of vincristine, dexamethasone, and cyclophosphamide, and the lymphoma maintenance regimen is monthly high-dose cyclophosphamide, vincristine, and dexamethasone.

Brecher and co-workers reported preliminary results of the induction and antileukemia-like maintenance regimen, described above, in 31 children with NHL (33). Three of four stage I patients and all nine stage II patients were in continuous remission for varying periods. Four of six stage III patients were in remission from 5 to 29 months, but six of eight stage IV patients died and one had a recurrence. Because of the poor results with the stage IV patients, the additional high-dose methotrexate intensification is being added. Further studies and longer followup will be necessary to determine if the high-dose methotrexate will improve results significantly in stage IV patients.

Sidney Farber Cancer Center, Jaffe and Co-workers

Since approximately 1973, Jaffe and his colleagues have been using a combined modality approach, basing treatment on stage of disease using a modified Ann Arbor staging system (38). All patients receive chemotherapy (table 1) with adriamycin, prednisone, and vincristine (APO). Stage I–II patients also receive adequate involved-field radiotherapy during induction. Following consolidation,

[8]Sullivan MP. Personal communication.
[9]Jenkin RDT. Personal communication.
[10]Tefft M. Personal communication.

all patients receive CNS prophylaxis with cranial irradiation and intrathecal methotrexate. Chemotherapy is continued for 2 years. Seventy-five percent of 30 patients treated so far with this approach are in continued remission, for periods from 5 to 32 months from diagnosis.[11]

NCI, Ziegler and Co-workers

For patients with diffuse undifferentiated Burkitt-type or histiocytic NHL the COMP protocol outlined in table 1 is used.[12] Remissions are unmaintained. Patients who relapse are eligible for ablative therapy with high-dose cyclophosphamide, cytosine arabinoside, 6-thioguanine, and BCNU (BACT) followed by bone marrow autografting.[12]

DISCUSSION

The survival reported from nine recent series of childhood NHL is shown in table 2. The staging has been almost always based on retrospective analysis, and the staging classifications used were not uniform, so that the results by stage are only roughly comparable. Furthermore, with the exception of Aur's series and Wollner's more recent patients, the therapy in nearly all series was non-uniform, reflecting the evolution of treatment philosophies over a period of years in a single institution. Nevertheless, certain facts are apparent. Conventional therapy over the past 2 decades has cured roughly one third of all children with NHL (1–3,8,21). Survival of children with localized disease is uniformly superior to that of children with generalized disease. Approximately 80%–100% of stage I patients are curable if an intensive multiple-drug chemotherapy regimen is combined with radiation (4,8,24) (*see* footnote 5). The survival has been improving in recent years, and preliminary results of trials in progress promise further improvement.

Future advances in management of childhood NHL are unlikely to result from transfer of therapeutic innovations introduced in the treatment of adults with NHL. In addition to obvious differences in histology and clinical behavior, there exist a number of examples of differences in chemotherapeutic sensitivity between adults and children. For example, DeVita and co-workers reported a 41% CR rate and 38% cure of adults with advanced diffuse histiocytic lymphoma by the use of combination chemotherapy with mechlorethamine (or cyclophosphamide), procarbazine, vincristine, and prednisone (39). The response in 15 children with NHL treated with the same cyclic combination (COPP) was far less impressive because only four patients were able to complete five or more cycles before disease extension became evident, and only two children achieved a CR.[13] At SJCRH, nine children with advanced lymphomatous relapse of NHL received the combination of vinblastine, bleomycin, and CCNU, and none achieved an objective response (*see* footnote 7). More effective combinations of new agents are needed for treatment of children whose disease is unresponsive to primary therapy.

Future efforts should be directed at recognizing identifiable subgroups of patients for appropriate treatment strategies through evaluation using a combination of staging procedures and histopathology. Identification of functional or immunologic features of tumor cells may also provide clinically relevant information. Further intensification of aggressive combined modality regimens is likely to expand the spectrum of long-term adverse late effects of cytotoxic chemotherapy and radiation in the growing child, including the risk of second tumors in survivors. Results of clinical trials currently in progress should help to clarify optimal management of childhood NHL.

LIST OF COMPOUNDS

Adriamycin: NSC-123127: CAS reg. No. 23214-92-8
L-Asparaginase: NSC-109229; CAS reg. No. 9015-68-3
BCNU: NSC-409962; CAS reg. No. 154-93-8; urea, 1,3-bis(2-chloroethyl)-1-nitroso-
Citrovorum factor: NSC-3590; CAS reg. No. 6055-86-5; glutamic acid, *N*-[*p*-[[(2-amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxy-6-pteridinyl)methyl]amino]benzoyl]-, calcium salt
Cytosine arabinoside: NSC-63878; CAS reg. No. 69-74-9; cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride
Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate
Dexamethasone: NSC-34521; CAS reg. No. 50-02-2; pregna-1,4-diene-3,20-dione, 9-fluoro-11β,17,21-trihydroxy-16α-methyl-
Mechlorethamine: NSC-762; CAS reg. No. 55-86-7; diethylamine, 2,2′-dichloro-*N*-methyl-, hydrochloride
6-Mercaptopurine: NSC-755; CAS reg. No. 6112-76-1; purine-6-thiol, monohydrate
Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-
Prednisone: NSC-10023; CAS reg. No. 53-03-2; pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-
Procarbazine: NSC-77213; CAS reg. No. 491-88-3; *p*-toluamide, *N*-isopropyl-α-(2-methylhydrazino)-, monohydrochloride
6-Thioguanine: NSC-752; CAS reg. No. 1832-72-0; purine-6-thiol, 2-amino-
Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1)

[11]Jaffe N. Personal communication.
[12]Ziegler J. Personal communication.
[13]Hartman JR, and Chard R. Personal communication, CCSG, Protocol No. 713.

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DISCUSSION IV: Other Treatment of the Non-Hodgkin's Lymphomas [1,*]

Dr. Hellman: I have asked Dr. Eli Glatstein to comment on the Stanford results with total lymphoid irradiation in patients with stage III disease.

Dr. Glatstein: We reviewed our results with total lymphoid radiotherapy in 51 patients with nodular lymphoma seen between 1961 and 1972. Treatment was much like total-nodal irradiation used in Hodgkin's disease. Very few patients had whole-abdominal treatment. The survival achieved in these patients is comparable to anything obtained with COP (cyclophosphamide, vincristine, and prednisone) or whole-body irradiation. The 5-year survival (actuarial) is 75% and the 10-year survival (actuarial) is 65%. The relapse-free survival is 44% at 5 years and 33% at 10 years—a significant achievement. Moreover, the most common site of failure was lymph nodes, often untreated, specifically epitrochlear, brachial, occasionally preauricular, and occasionally orbital. The patients who relapsed in those eccentric sites and other patients who received a second course of radiotherapy and achieved a second remission have not required any form of systemic management. Of the original 51, 60% were followed over a 10-year period and were restaged, although not all had repeat bone marrow (the bone marrow was negative in the first place). The staging was clinical with one bone marrow biopsy. Results in patients with diffuse histology were poor; the relapse-free survival in stage III, lumping all of the diffuse categories together, was just < 20% at 5 years and flat.

Dr. Smith: Dr. Murphy, you said five of 23 patients in an older study had developed CNS disease. Did any of them receive cranial irradiation for prophylaxis?

Dr. Murphy: They all had received cranial irradiation plus intrathecal methotrexate. The point I wished to make was that despite prophylaxis they developed CNS disease as their initial site of failure.

Dr. Smith: Of the six patients who died in your latest study, did any relapse in the CNS first?

Dr. Murphy: CNS disease was not a principal cause of death. Of the six, three patients failed to achieve remission, two had early lymphomatous recurrences and did not respond to further therapy, and the last had a simultaneous systemic and CNS initial relapse.

Dr. Lowenthall: In a paper presented at this meeting we heard that 81% of the patients who had complete remissions relapsed and did so in the lymph nodes. If most of those relapses occurred in sites of initial bulky diseases, as I suspect, is anyone using adjuvant radiotherapy at the sites of initial bulky disease to prevent such relapses?

Dr. Hellman: Your question concerns patients who have non-localized disease?

Dr. Lowenthall: Yes.

Dr. Hellman: The National Cancer Institute of Canada is running a trial in which part of the protocol employs combination chemotherapy and irradiation of bulky disease in patients who have responded or partially responded.

Dr. Lowenthall: Can you say anything about the results?

Dr. Hellman: No, this trial is only just getting under way. The protocol assumes that the major risk of failure is at the site of bulky disease.

Audience: It is correct that most relapses occur in nodes. It is also true that the majority of these patients have bulky disease in nodal sites where they relapse. The same phenomenon occurs in Hodgkin's disease. A number of current studies are addressing themselves to that fact. For example, Dr. Portlock mentioned that in his studies the concomitant use of total-nodal irradiation and combination chemotherapy has been less than satisfactory.

Dr. Rappaport: Dr. Chaffey, in the patient who had total-body irradiation, did you consider giving a booster to areas of gross disease after the total-body irradiation? Did you encounter any cataracts in this group?

Dr. Chaffey: Yes, in the 15% of patients who had bulky disease that could be localized, we "boosted" those areas to doses between 1000 and 2000 rads. The remainder had such generalized disease that it did not seem worthwhile to boost local areas and we did not want to treat them extensively. We

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[1]The following investigators participated in this discussion: *S. Hellman* (chairman) and *J. T. Chaffey* (Sidney Farber Cancer Institute, Harvard Medical School, Boston, Mass); *E. Glatstein* (Stanford University School of Medicine, Calif); *Dr. Smith* (Oakland, Calif); *S. Murphy* (St. Jude Children's Research Hospital, Memphis, Tenn); *Dr. Lowenthall* (Australia); *L. Grossman* (Vancouver, Canada); *H. Rappaport* (University of Chicago School of Medicine, Ill); *L. M. Fuller* and *M. P. Sullivan* (The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston); *G. J. D'Angio* (Memorial Sloan-Kettering Cancer Center, New York, NY); and *R. C. Young* (National Cancer Institute, Bethesda, Md).

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have seen no cataracts in these patients and I would not have expected to do so with such a low dose and low dose rate.

Dr. Rappaport: Dr. Fuller, since abdominal disease seems to be of great importance and since chemotherapy is also failing to control it, would it be feasible to treat the larger fields with what we once called a "spray" dose? In most patients this amounts to about 2500 rads. Then a booster would be added only to areas of gross disease, keeping the field to a minimum. Has this been tried?

Dr. Fuller: That is what we do. We give a 3000-rad dose to the total abdomen and then reduce the field to the residual disease. In nodular lymphomas this approach is very effective, particularly for the poorly differentiated lymphocytic variety. With this approach we have about a 60% complete remission rate with permanent disappearance of disease from the abdomen. That includes both the good and the bad presentations. This approach does not work in diffuse lymphomas which are almost all histiocytic. The response to this kind of treatment is very poor, and in our studies 64% of patients had local failures. In the diffuse lymphomas we put the emphasis on the chemotherapy, both to control local disease and to prevent dissemination. When you do this, you must reduce the treatment field to conserve the bone marrow; in other words, rather than cut the dose, we cut the treatment field to the known bulky disease.

Dr. Rappaport: My last question concerns the Memorial Hospital study. I understand that radiotherapy to areas of gross disease other than the mediastinum was limited to a dose of 1500 rads.

Dr. D'Angio: Concerning the role of radiation therapy in the Memorial Hospital program, in general the policy was to irradiate areas of bulky disease, namely those measuring ≥ 5 cm at the time of diagnosis. This was usually done after shrinkage of the mass. Doses of about 3000 rads were adequate in that they achieved local control and the diseases did not recur in those areas. Higher doses were no more effective. However, such control made no difference in survival. In summary then, local booster radiation of about 3000 rads or so prevents local recurrence but does not improve survival.

Dr. Hellman: Dr. D'Angio, do you want to say anything about the distribution of the sites of initial presentation? I believe your series was unusual because it contained many nodular lymphomas and many other atypical presentations.

Dr. D'Angio: I'm sorry. I don't know how many of these cases might have been called "leukemia" by other groups.

Dr. Grossman: I have two questions for Dr. Murphy. First, why did you choose 25% as the cut-off when classifying patients as either leukemia or lymphoma? Can you speculate on why children who present with bulky disease and leukemia do better than those who present with bulky disease only? In the adult the opposite situation seems to obtain.

Dr. Murphy: The distinction between lymphoma with initial marrow involvement and leukemia with a bulky mass at diagnosis is quite arbitrary in some cases. We chose 25% because it usually defines the M3 marrow which is generally considered to be the on-study requirement for most leukemia protocols. Concerning the second question, I really don't know why children who have bone marrow involvement survive longer.

Concerning the Stanford study that Dr. Portlock presented, I don't think the rationale was made clear for what I usually refer to as "Operation Overkill," the combination of intensive chemotherapy with high-dose total-nodal radiation. We were aware that most of the failures occurred in lymph nodes, and we presumed that the effectiveness of chemotherapy would be related to blood flow. It is a simple physiologic fact that the blood flow per gram of tissue is lower in lymph nodes than in almost any other organ in the body. We made a few tactical errors in setting up this study because we did not restage the bone marrow in these patients (almost all had positive bone marrows initially). First, we should not have committed these children to intensive radiation without confirming that the marrow was under control. Second, the intensity of radiation was clearly open to question. In most instances we gave 4400 rads or up to 4400 rads until we had to stop, and most of those patients did not get additional chemotherapy. However, with some revisions the approach is still a feasible one and may actually make some contributions in this area although the data do not show it, chiefly because of the failure to restage the bone marrow.

Dr. Sullivan: I would like to endorse Dr. Woolner's protocol. We started using it at the M. D. Anderson Hospital 2 years ago and now 30 patients have been treated according to his protocol. I might point out that it is not suitable for previously treated patients or for those with Burkitt's lymphoma.

Dr. Rappaport: I believe Dr. Murphy said that 15% of the lymphomas in the Memorial Hospital series were nodular, and that this incidence was excessive. It is not excessive; I suspect that some of these tumors may have been reactive follicular hyperplasia and others may not have been nodular lymphoma.

Dr. Hellman: Perhaps we should close the discussion on the Memorial Hospital series since Dr.

Woolner is not here. I have a question for Dr. Young. Were the relapse-free survivors in your randomized study between chemotherapy and radiotherapy treated with total-body irradiation or total-nodal irradiation?

Dr. Young: It was all groups combined.

Dr. Hellman: Was there any difference?

Dr. Young: No, there did not seem to be any difference. The numbers get very small—only 11 patients were treated with total-nodal irradiation, but relapse-free survival rates did not show any difference.

Immunologic Classification of Non-Hodgkin's Lymphomas: Current Status [1]

Maxime Seligmann,* Jean-Claude Brouet, and Jean-Louis Preud'homme [2]

An attempt to improve the classification of non-Hodgkin's lymphomas according to cell-membrane characteristics is justified for two main reasons. First, we are dealing with multiple disease entities that are not grouped under any universally accepted pathologic classification at present, a situation that precludes valid clinical analysis and therapy; and second, the study of the surface markers of proliferating cells has led to an improved classification of other hematologic malignancies (1). Such studies have made it possible (*a*) to lump together the Sézary syndrome and mycosis fungoides, which are both T-derived proliferations (2,3); (*b*) to unmask the heterogeneity of acute lymphoblastic leukemias, a finding which may prove useful in selecting therapeutic regimens for the various groups of patients (4); (*c*) to define a small subset of chronic lymphocytic leukemias which are T derived and often present with peculiar clinical and hematologic features (5); and (*d*) to assign a common clonal origin to supervening acute malignancies and previous chronic lymphoid proliferations (ie, acute blastic transformation of chronic lymphocytic leukemia) (6).

The demarcation between B- and T-lymphocyte markers is less clearcut than earlier work had suggested. The existence of subpopulations of B and T cells with distinct markers and functions, which was well established in mice, becomes increasingly important in man. Several additional points are worth considering in the study of membrane phenotypes of lymphomatous cells which are malignant but have limited capabilities to undergo further differentiation. B and T cells may express different markers according to the cell cycle and to the various stages along their differentiation pathway. Neoplastic cells may undergo surface changes and lose some normal membrane markers or, conversely, may express new markers or retain markers characteristic of undifferentiated cells, if such cells were stimulated by the neoplastic changes. Thus, it should be stressed that a classification which would appear to be reliable for markers of normal lymphocytes may not be valid when extrapolated to lymphomatous cells; also, it should be noted that the membrane phenotype of the lymphoma cells does not necessarily identify the "target cell for the neoplastic event." With these reservations in mind, the study of surface markers can provide new information on the nature of lymphoma cells and perhaps lead to a more rational categorization of these diseases. However, the reliability of the results of such studies depends upon an awareness of a number of methodologic problems and pitfalls.

METHODOLOGIC PROBLEMS AND PITFALLS

It is obvious that the pathologist has to study the markers of the tumor cells themselves and not those of the presumably normal surrounding cells. Therefore, the elegant methods set up by Jaffe et al (7) on frozen sections can be applied only to cases with a nodular pattern or to tissues with an overwhelming homogeneous population of lymphoma cells. The study of cell suspensions allows us to assess the morphology of the individual cells with given surface markers.

Immunoglobulins (Ig)

Membrane-bound Ig detectable by immunofluorescence constitutes the most reliable marker of B cells and represents a clonal marker of B-cell proliferations when the procedure uses truly monospecific antisera to the various Ig chains (8). However, one should be aware of a number of technical pitfalls (9). Nonspecific staining may result from the presence of damaged cells or Ig aggregates in the reagents. The mere presence of Ig molecules at the surface of a cell does not necessarily mean that these molecules are produced by that cell. Monocytes and other nonlymphocytic cells which possess

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an Fc receptor may bind IgG from the serum or from the reagents. The main reasons for the detection of extrinsic Ig on lymphoid cells are the presence of labile cytophilic IgG, the attachment of immune complexes, and the binding of antibodies to membrane antigens, such as antibodies directed towards leukemia- or lymphoma-associated surface antigens. It is therefore of the utmost importance in the study of membrane-bound Ig to identify properly the positive cells and to use F(ab')2 reagents of proven monospecificity. The detection of surface IgD and, for the other Ig classes, of a single class of heavy chain and a single type of light chain suggests that the Ig is an actual cell product but does not rule out the possibility that one is dealing with extrinsic Ig. For instance, antibodies to membrane cell antigens may be rather homogeneous, and in vitro experiments may be required to ensure that the surface Ig was synthesized by the cells under study (8).

Intracytoplasmic Ig is considered to be a reliable B-cell marker since only B cells produce Ig. However, Mason et al[3] have recently shown that the sensitive immunoperoxidase three-stage technique applied to fixed human leukocyte smears can detect membrane-bound IgM and IgD in B cells, and IgG molecules in approximately 25% of normal lymphoid cells; this finding probably represents Fc-receptor-bearing lymphoid cells with bound serum IgG. Moreover, IgG was demonstrated within normal human monocytes. These findings prompt reassessment of recent reports describing the detection by this technique of Ig in lymphoma and Reed-Sternberg cells, particularly in view of the fact that the Ig molecules found in Sternberg cells appeared to be mainly IgG with both light-chain types (10).

Other Markers

Some classic B-cell markers such as the receptors for the complement components and the Fc of IgG are not specific for B cells. The receptor for the Fc portion of IgG is present on monocytes, on the so-called third population of lymphoid cells, and on a subset of T cells which appear to have a suppressor activity. Complement receptors are expressed on monocytes and on a small subpopulation of T cells, especially on thymocytes (11). In addition, it has been demonstrated that the majority of human T cells bear a receptor for IgM (12) and some of these cells may occasionally give positive reactions in the EAC rosette test. Some other B-cell characteristics, such as the formation of rosettes with mouse erythrocytes, are found only on a subpopulation of B cells; this test is positive with most chronic lymphocytic leukemia cells but negative with most lymphomatous B cells (13). The presence of Ia type of antigen, revealed by alloantisera or heteroantisera on leukemic cells (14–16), should not be considered as a B-cell marker since, for example, the Ia antigens are expressed by acute myeloblastic leukemia cells.

Heteroantisera revealing specific B or T antigens may constitute useful markers in the membrane phenotyping of lymphoma cells. Some such antisera can be used only in cytotoxicity tests because they are only relatively specific. This procedure is not satisfactory since it does not allow simultaneous checking of other markers or direct examination of the positive cells. In addition, the sensitivity of cytotoxicity tests may vary greatly between normal lymphocytes and malignant cells. Immunofluorescence is, therefore, by far the most reliable procedure, but at the level of sensitivity of this method, truly specific antisera are not easy to obtain. Some such antisera react only with subsets of B or T cells. In addition, one should be cautious in interpreting the results obtained with antisera to B or T fetal or neoplastic cells when applied to the study of lymphomatous cells; these may express fetal derepressed or tumor-associated antigens. The problems related to the detection and the meaning of leukemia-associated or -specific antigens will not be discussed here since this approach has not yet been applied to human lymphomas.

MEMBRANE MARKERS OF MALIGNANT CELLS IN HUMAN NON-HODGKIN'S LYMPHOMAS

Immunologic studies have provided definite confirmation of pathologic and clinical findings in some groups of lymphomas such as well-differentiated diffuse lymphocytic, nodular, and Burkitt's lymphomas which are all monoclonal B-cell malignancies.

The close relationship between well-differentiated diffuse lymphocytic lymphoma and chronic lymphocytic leukemia was confirmed when the same membrane markers were found on lymphocytes from both groups of patients. In those cases without any serum monoclonal Ig, the low density of the surface Ig, belonging in most cases to the IgM class, and the uniform and faint fluorescence pattern of all the proliferating lymphocytes (17) agree with the hypothesis that their development was arrested at the same and relatively early stage in the B-cell line pathway (18). In occasional patients, this block

[3]Mason DY, Labaume S, and Preud'homme JL. The detection of membrane and cytoplasmic immunoglobulins in human leukocytes by immunoperoxidase staining. Clin Exp Immunol. In press.

in the maturation process is incomplete and a small amount of monoclonal Ig is secreted in the serum.

The results of immunologic studies in the nodular lymphomas have supported the views of Lennert (19) and of Collins and Lukes (20), who proposed, on the basis of morphologic studies, that these lymphomas arise from follicular center cells. Apart from very rare reports of T-derived nodular lymphomas (21,22), practically all tumors studied thus far in various laboratories, regardless of the cytologic subtype and of the degree of nodularity, have proved to be B-derived malignancies with usually a high density of Ig molecules bound to the membrane of the lymphomatous cells. These cells also bear C3 receptors similar to the predominant cell of the lymphoid follicle (23).

The neoplastic cells from African cases of Burkitt's lymphoma were evaluated for surface markers and glucose-6-phosphate dehydrogenase, and this disease was shown to be a monoclonal B-cell proliferation (24). Similar surface characteristics were found on Burkitt's tumor cells in French and American patients whose disease presented as lymphoma (25) or as acute leukemia (26). Although the neoplastic cells of both endemic and nonendemic cases are cytologically and immunologically indistinguishable, we don't know if we are dealing with the same disease caused by the same agent. It should also be stressed that, although Burkitt's lymphoma is defined by precise morphologic and immunologic characteristics, its course varies considerably from patient to patient. In some patients, survival is prolonged, and probably some achieve cure following chemotherapy; others run a fulminating course and treatment is ineffectual. This great variability in evolution outlines the limited prognostic value of surface markers and histology in non-Hodgkin's lymphoma.

Most diffuse poorly differentiated lymphocytic lymphomas in adults are B-cell malignancies (7,22,27,28). This appears to be the rule when these diffuse lymphomas are recognized morphologically to be of follicular center cell origin from the presence of cleaved cells (29). In roughly 10% of the patients, the neoplastic cells had T-surface characteristics and in a similar percentage no membrane markers were detectable.

Immunologic studies have helped to define childhood lymphoblastic lymphoma (30,31), a subgroup of childhood lymphomas which was previously included in the diffuse poorly differentiated lymphocytic lymphomas. The proliferating cells may have a convoluted appearance (32), but this feature is not constant (30). The presence of an anterior mediastinal mass in many of these children suggests that these tumors may be of thymic origin. Many of these cases have shown T-lymphocytic markers on the neoplastic cells (11,31–35), and several groups (11,31,35) have reported complement receptors on these neoplastic T-lymphoid cells (as on the thymic cells). Cytochemical studies indicate a strong positivity of the proliferating cells for acid phosphatase (11). Leukemia develops rapidly in many of these patients and these childhood lymphoblastic lymphomas share many morphologic, cytochemical, and clinical features with the T-derived subgroup of acute lymphoblastic leukemia (4,36,37). On the basis of both clinical and immunologic data, these two diseases are closely related and may represent different manifestations of the same neoplastic process.

Diffuse large cell (histiocytic) lymphomas appear immunologically to represent a heterogeneous group. Table 1 summarizes the results obtained in our laboratory during the study of membrane markers of the malignant cells in the lymph nodes of 17 patients with diffuse large cell lymphomas. These results agree with most data recently published (38,39). Only occasional cases of histiocytic lymphomas may be truly related to the monocytic series. The study of membrane markers has provided suggestive evidence in favor of this hypothesis in a few patients (22,38), and in one instance (40), in vitro culture of such lymphomatous cells has proved that they were able to synthesize lysozyme. Fifty to sixty percent of large cell lymphomas appear to originate from B cells. In our series, five of the eight cases that were of monoclonal B-cell origin arose in patients previously affected with chronic lymphocytic leukemia, Waldenström's macroglobulinemia, α-chain disease, or follicular lymphoma, which are lymphoproliferative diseases of well-documented B-cell origin. Our results strongly suggest that, in such patients, the supervening large cell lymphoma does not represent the emergence of a second malignant clone but is related to the original B-cell proliferation (38). T-cell-derived large cell lymphomas appear to be infrequent since they account for $< 10\%$ of the cases. In $> 30\%$ of the patients, the large lymphomatous cells are devoid of the usual membrane markers of mature B or T lymphocytes. In our hands, the use of specific heteroantisera to T or B cells in these unclassified cases did not give further evidence concerning the cellular origin. An analogous situation exists in 70% of the patients with acute lymphoblastic leukemia (4), the blast cells of which contain deoxyterminal nucleotide transferase and bear antigens of the Ia type. Lymphoid stem cells may be devoid of the usual T- or B-membrane markers.

In lymphomas with a mixture of small and large cells (mixed lymphocytic-histiocytic type of Rappa-

TABLE 1.—Heterogeneity of membrane markers of malignant cells in 17 diffuse large cell lymphomas

B-cell properties	8*
T-cell properties	2
Probable monocytic origin	1
No detectable marker	6

*Supervening on previous chronic B-cell proliferations in 5 cases.

port's classification), both cell types share the same surface markers or both lack B- and T-membrane markers.

There are some indications that those patients with diffuse lymphomas whose malignant cells demonstrate B-membrane markers may survive longer than the other patients (41). The study of many more patients treated in an identical manner within the various morphologic subgroups is warranted in order to evaluate the possible prognostic significance of the membrane markers. This evaluation is of special importance for the large cell lymphomas where long survivals are obtained in 25%–30% of the cases after intensive chemotherapy, as shown by various papers in this issue. Further studies will indicate whether or not the lymphomas of these patients belong to a specific immunologic subgroup.

CONCLUSION

The study of immunologic markers has already led to an improvement of our knowledge of non-Hodgkin's lymphomas. These studies may be useful in distinguishing between reactive hyperplasia and malignant proliferation. They help us to identify the origin of the proliferating lymphomatous cells and may give some indication concerning the nature of the target cell which was hit by the neoplastic event. The results of these studies have contributed to the recognition of some distinct disease entities within non-Hodgkin's lymphomas such as the lymphoblastic lymphoma of childhood, Burkitt's lymphoma, B-derived large cell lymphoma supervening on chronic B-cell proliferations, etc. In the future, better knowledge of the membrane markers of lymphomatous cells may lead to some improvement in therapy and in the monitoring of these patients. This goal could be achieved in the distant future by various immunomanipulations if studies of tumor-associated antigens are extended to non-Hodgkin's lymphomas, but in the near future the principal contributions will come through more accurate classifications leading to better prediction of survival and choice of treatment. It is obvious that an immunologic classification per se cannot be satisfactory for clinical purposes since, for instance, B-derived lymphomas include the follicular lymphomas, Burkitt's lymphomas, immunoblastic lymphomas supervening on chronic lymphoid malignancies, etc. Any immunologic classification should, of course, be combined with a morphologic classification, and there is an urgent need for a workable and reproducible pathologic classification. Such a classification should take into account the information provided by the study of membrane markers since no example in clinical medicine suggests that scientific accuracy precludes better clinical analysis and improved therapy.

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Curability of Non-Hodgkin's Lymphomas[1]

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SUMMARY

The relapse rates of patients with malignant lymphoma have been analyzed in relation to the number of patients in complete remission (CR) at yearly intervals after the onset of therapy. Several different patterns of relapse have been identified. Patients in CR from nodular poorly differentiated lymphocytic lymphoma have a low rate of recurrent disease (14%) during the first year of treatment but rates of relapse in succeeding years have not decreased. Patients with diffuse poorly differentiated lymphocytic lymphoma have a significantly higher relapse rate during the first year of treatment (33%). However, remission duration curves suggest that the risk of relapse is decreasing with time. Patients with diffuse histiocytic lymphoma, who initially have the greatest risk of disease recurrence (42%), subsequently showed a significant fall in their rate of relapse. As many as 50% of these patients who attain a CR may have been cured of their disease. An analysis of CR duration curves may be used to determine the effective doubling time of various malignant diseases and to estimate cure rates within a few years after the onset of therapy.

[Cancer Treat Rep 61:1185–1190, 1977]

A discussion of the curability of non-Hodgkin's lymphoma indicates a higher goal than the mere palliation of malignant lymphoma. Indeed, we can now begin to seriously consider the possibility of cure. This broadening of perspective is a consequence of recent advances in therapy, and of the increasingly more optimistic outlook of physicians who treat malignant lymphomas and of their patients.

In the early 1960s, little more than half of our patients were responding to conventional single-agent chemotherapeutic programs and only 25% attained a complete remission (CR) (1). Today, Bitran et al have reported CR rates of > 90% among patients with stage I and II diffuse histiocytic lymphoma (DHL) following extended radiation therapy (2). Similarly, among patients with stage III and IV disease, adriamycin combination chemotherapy (CHOP)[3] has produced CRs in > 75% of patients with nodular lymphocytic lymphoma (NLL) and in > 55% of patients with diffuse disease (3); good responses have also been achieved with the BACOP combination (4).[4] Thus, it is entirely appropriate to question if now or in the near future we will be able to achieve a cure in some of our patients with malignant lymphoma.

The requirements for cure in malignant disease are formidable indeed. Curative therapy must reduce the number of viable malignant cells to such an extent that regrowth sufficient to produce subsequent relapse does not occur. Studies by Skipper et al (5) have demonstrated that a single malignant cell is capable of producing fatal disease. They point out that a focus of tumor only 1 mm in diameter may contain as many as 10^6 cells, that 1 g of tumor containing 10^9 or 1 billion cells may often be present before disease becomes clinically apparent, and that before the lethal stage of malignant

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[3] CHOP = cyclophosphamide, adriamycin, vincristine, and prednisone.

[4] BACOP = bleomycin, adriamycin, cyclophosphamide, vincristine, and prednisone.

disease, the number of tumor cells may increase to > 1 trillion or 10^{12} (6). Clearly, the demands placed upon any treatment program are great if we must eliminate virtually the last cell in order to achieve a clinical cure.

Basic studies by Skipper et al, Schabel, and Goldin et al (5–8) have identified certain fundamental principles of chemotherapeutic action which may guide us in our attempts to attain clinical cure. Of particular interest is the observation that chemotherapeutic programs follow first-order kinetics in killing tumor cells; that is, a constant percentage of the tumor cell population is affected by any given chemotherapeutic program (5). Since the chemotherapeutic agents available today have a relatively low log kill, these theoretic considerations lead to two practical conclusions. First, a combination of active agents or modalities will be required to approach clinical cure. Second, since the ability to cure a malignant disease appears to be directly related to the number of viable tumor cells, it follows that the best results will be achieved in patients with limited disease. Recent clinical trials have supported these conclusions.

Currently, a number of chemotherapeutic agents have shown activity against malignant lymphoma, namely the alkylating agents, the vinca alkaloids, prednisone, antibiotics such as adriamycin and bleomycin, the nitrosoureas, and other antimetabolic drugs. Unfortunately, because these chemotherapeutic agents have limited efficacy, the number of CRs achieved with single-drug treatment is relatively small. In a review of patients with extensive disease treated with either a single alkylating agent, vincristine, or prednisone, Jones et al (1) observed CR rates ranging from 5% in DHL to 48% in patients with nodular poorly differentiated lymphocytic disease (NPDL). Less than 25% of all patients with diffuse lymphoma achieved CRs and < 40% of patients with nodular disease had CRs.

In contrast, combination chemotherapy programs have produced a more than twofold increase in the number of CRs (table 1). The advantage of combination chemotherapy is seen among large heterogeneous groups with malignant lymphoma and also among more restrictive categories and in each individual pathologic type. With CHOP chemotherapy, 55% of patients with diffuse lymphoma and 77% of those with nodular lymphoma achieved a CR (3). Schein et al (9) achieved a 60% CR rate with CVP or MOPP[5] chemotherapy in patients with NPDL and Stein et al (10) obtained a 79% CR rate with COPP[6] therapy in a similar group of patients.

A corresponding improvement in remission duration and survival has also been demonstrated among patients in certain pathologic categories. In advanced DHL, the median duration of response following single alkylating agent therapy was approximately 5 months and the median survival

[5] CVP (or COP) = cyclophosphamide, vincristine, and prednisone.
MOPP = mechlorethamine, vincristine, prednisone, and procarbazine.

[6] COPP = cyclophosphamide, vincristine, prednisone, and procarbazine.

TABLE 1.—Response to combination chemotherapy*

Treatment	Study group	% in CR	
		Lymphocytic lymphoma	Histiocytic lymphoma
CHOP	SWOG	72	52
COP-bleomycin	SWOG	69	64
CVP	NCI	57	—
Cyclophosphamide-vincristine-methotrexate-cytosine arabinoside	Yale University	—	60
HOP†	SWOG	55	57
COP-cytosine arabinoside	SWOG	55	37
MOPP	SWOG	49	31
MOPP	NCI	48	38
COP	SWOG	47	37
COP	ECOG-ALGB‡	35	31

*Includes data from refs 16, 17, 21–23.
†HOP = adriamycin, vincristine, and prednisone.
‡Eastern Cooperative Oncology Group-Acute Leukemia Group B.

with both radiation and single-drug chemotherapy was < 1 year (1). With CHOP chemotherapy (3), we project that the duration of CR will be > 2 years. Indeed, DeVita et al (11) have reported a median duration of CR of > 3 years among patients with DHL responding to MOPP or COPP chemotherapy. Correspondingly prolonged survival times have also been demonstrated, not only with chemotherapy, but also following radiation treatment; for example, Bitran et al (2) observed a median survival of > 5 years among 20 patients with stage I or II DHL following involved or extended-field radiotherapy. Thus, many studies have confirmed the theoretic benefits of combination chemotherapy and of aggressive treatment in limited disease.

Documentation of long-term success in the treatment of patients with malignant lymphoma requires a rigorous analysis of the degree and quality of this success. But are the data sufficient to estimate a rate of cure or to indicate in which pathologic type a cure may be near? Frei and Gehan (12) have emphasized the inverse correlation between the risk of relapse and potential cure. In each of the studies they analyzed, the risk of relapse was greatest early in treatment and fell progressively with time. These observations suggest that patients who were free of disease for > 4 years had at least an 80% chance of cure.

This type of analysis requires a uniform patient population with tumors that exhibit similar growth kinetics and relapse characteristics, and it appears that such subgroupings can best be defined by the Rappaport classification (13). Unfortunately, only a few studies using the Rappaport classification include long-term followup data.

If we consider the relative relapse rate of patients with different pathologic types of malignant lymphoma, three distinctive patterns of relapse become evident. Table 2 shows the relative relapse rate of patients with stage III and IV malignant lymphoma in relation to the number of patients in CR at the start of each year of treatment. This table compares adriamycin combination chemotherapy, CHOP (3), and other combination chemotherapy programs not containing adriamycin. Patients with NPDL had the lowest rate of relapse during the first year of treatment, in sharp contrast to that observed among those with Hodgkin's disease. Although the rate of recurrent disease following CHOP therapy has been somewhat lower than that seen after

TABLE 2.—% of patients relapsing during the respective years after the onset of treatment*

Histologic type†	Treatment	No. of patients	% of patients relapsing			
			Yr of treatment			
			1	2	3	4
NPDL	CHOP	41	8	17	16	—
	Combination chemotherapy	31	24	44	36	—
	Total	72	14	28	21	—
NM	CHOP	5	33	36	—	—
	Combination chemotherapy	19	14	16	16	—
	Total	24	20	22	—	—
DWDL	CHOP	11	18	42	—	—
	COP	16	21	21	—	—
	Total	27	20	32	—	—
DPDL	CHOP	23	26	30	—	—
	COP	46	37	20	32	—
	Total	69	33	27	32	—
DM	CHOP	6	30	24	—	—
	COP	14	12	22	—	—
	Total	20	20	23	—	—
DHL	CHOP	37	33	27	2	—
	Combination chemotherapy	89	29	11	10	0
	Radiation therapy (Stanford data)	62	65	9	6	—
		—	—	—	—	—
	Total	188	42	14	7	0

*Includes data from ref 3 (CHOP), refs 9, 11, 14–17 (combination chemotherapy), and ref 18 (radiation therapy).

†NM = nodular mixed; DWDL = diffuse well-differentiated lymphocytic; and DM = diffuse mixed.

other combinations, these patients continue to relapse with time. There is as yet no indication that the rate of relapse is reduced after ≥ 1 year of CR.

The pattern of relapse is somewhat different among patients with diffuse poorly differentiated lymphocytic lymphoma (DPDL). The rate of relapse during the first year of treatment is significantly greater ($P < 0.01$) than in NPDL. Furthermore, the relapse rates following CHOP chemotherapy are comparable to those seen with the earlier combination programs. Again, we have seen no significant diminution of the rate of relapse with time.

Patients with DHL also have a different pattern of relapse. The combination chemotherapy category (table 2) includes studies by Schein et al (9), DeVita et al (11), Berd et al (14), and Sweet et al (15), COP data from the SWOG (16,17), and relapse data for patients treated at Stanford with radiation therapy (18). These patients with DHL show a high rate of disease recurrence during the first year of treatment, particularly among those who received radiation therapy. Subsequently, there is a significant reduction in the yearly relapse rate. In contrast to those with lymphocytic lymphoma, patients with DHL show a continued reduction in relapse rate with time, so that after 2 years of treatment the risk of recurrence is < 10%. This observation will have to be confirmed with a longer followup, but it does appear that patients with DHL have a pattern of disease recurrence comparable to the one Frei and Gehan (12) observed in Hodgkin's disease.

The differences in patterns of relapse between the different pathologic types are brought out more clearly by comparing plots of the duration of CR (fig 1). The CR duration curve appears to be linear for patients with NPDL. Although NPDL is among the most responsive of pathologic types, we have not yet observed a flattening of the curve which would indicate a declining relapse rate and potential cure.

Patients with DPDL show a steeper remission duration curve because of a higher rate of relapse early in the course of treatment. The remission duration curve has another distinctive feature—its contour is that of a gradual concave arc. This may be a sign of an impending plateauing of the curve and of possible cure in some of these patients.

The slope of the remission duration curve in DHL shows a more dramatic and indeed a statistically significant change ($P = 0.05$). Patients with this disease have one of the poorest responses to current chemotherapy, and hence the initial portion of the remission duration curve has a steeper slope than other pathologic categories. However, after a relatively short period, the slope of the curve shows a marked change in the interval between 25 and 125 weeks which becomes maximal about 75 weeks following the onset of therapy. Thereafter, the rate of change is slower as the curve begins to plateau. This plateauing of the remission duration curve in DHL is comparable to that seen in Hodgkin's disease and suggests that a cure may have been achieved in a portion of these patients.

Skipper and Schabel have studied the relapse of malignant disease in animal systems (19,20) and have shown that in mouse acute leukemia one can predict the time of relapse if the number of viable tumor cells remaining after therapy and the prolif-

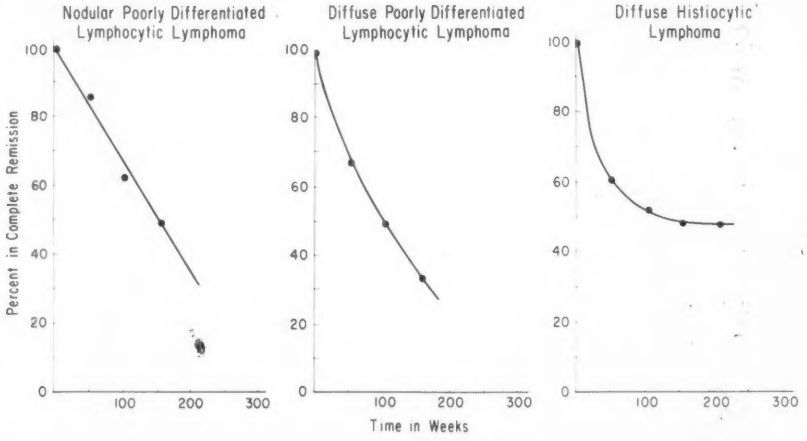

FIGURE 1.—Remission duration curves for patients with malignant lymphoma of different pathologic types.

erative rates of these malignant cells are known. Cumulative information obtained from these and other studies now permits a precise prediction of the relapse pattern in the experimental animal following a prescribed chemotherapeutic program; however, some variation persists in the observed time to relapse. Skipper and Schabel have concluded that the difference between observed and predicted relapse times represents variations in the proliferation rates of the tumor cell population which remains following therapy.

Two important conclusions from these animal studies have a direct bearing on clinical management. When a large number of viable malignant cells remain in the host after maximal benefit has been derived from therapy, the time to relapse can be predicted and should be proportional to the number of malignant cells. Under these circumstances, the remission duration or survival curve would be relatively linear. However, if the patient's tumor burden has been reduced to only a few residual cells, the time to relapse will be relatively longer because of the paucity of malignant cells and the longer doubling time of subpopulations of malignant cells. Under these circumstances, a rapid change in slope is followed by a terminal plateau in the remission duration curve. The "break" in the remission duration curve appears at the point where the maximum rate of change of slope occurs. In clinical terms, the patients who remain in CR when a break appears in the remission duration curve are those whose tumor burdens have been reduced to one or only a few malignant cells.

An analysis of our remission duration curves in light of these concepts permits several conclusions concerning the various pathologic categories of malignant lymphoma. NPDL exhibits one of the highest response rates to induction chemotherapy and the slope of the remission duration curve is initially more shallow than any of the other pathologic types. Yet in spite of the apparent responsiveness of NLL, no change in slope has yet been identified which would indicate a substantial reduction in tumor burden. This suggests that while the short-term prognosis for patients with NLL is quite good, current chemotherapy does not yet approach cure. In contrast, the gradual arc of the curve in DPDL may be significant; if this arc persists over longer periods of followup, it may indicate an impending break in the remission duration curve.

Such a break is clearly evident in the curve of patients with DHL; the slope of the curve begins to change after about 25 weeks and continues to 125 weeks (fig 2). This change reaches a maximum between 50 and 100 weeks. The midpoint of this interval, 75 weeks, is the point when the break may be said to occur. While this curve is based on preliminary data, such an analysis suggests that the disease burden will be reduced to a very few malignant cells in as many as 50% of patients with DHL who achieve a CR with induction therapy. These patients may achieve cure. Recent clinical reports of Bitran et al (2), Schein et al (9), DeVita et al (11), and others concerning long-term remissions observed among patients with DHL support this somewhat theoretic conclusion.

Skipper and Schabel have suggested that our remission curves reflect important information about the kinetics of tumor growth. If malignant disease is going to relapse at the break point in the remission duration curve, the few cells which remain following induction therapy must continue to divide until the tumor burden expresses itself clinically. This expression has been estimated to require approximately 30 doubling times in man. Thus, knowing the time when the break in the remission duration curve occurs, we can estimate the doubling time of the particular tumor involved. In DHL, a break appeared in the remission duration curve after 75 weeks. If this interval is required for 30 generation times, it follows that the effective dou-

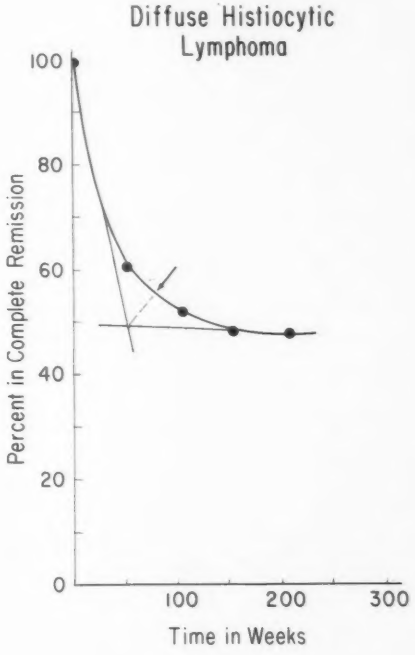

FIGURE 2.—Remission duration curve for patients with DHL.

bling time for DHL is approximately 17.5 days (range 12–23 days) and that the tumor would increase tenfold every 1.9 months. These findings are quite consistent with Skipper's analysis (20) of patients with DHL reported by DeVita et al (11). Clinically, this doubling time of 17.5 days indicates a rapidly growing malignancy and it is just this situation in which cycle-active agents and their combination chemotherapeutic programs would be most effective.

At present, a significant break in the remission duration curve has been found only in patients with DHL. However, these analytic techniques can be used to make projections for patients with other histologic types of disease. A change in slope of the remission duration curve has been observed for patients with DPDL. Extrapolation of the gradual arc of this curve would indicate a change in slope between 38 and 275 weeks, and a plateau after 300 weeks, with 15% of patients remaining in CR. The effective doubling time with this projection is approximately 28 days. This relatively longer doubling time for DPDL is consistent with its clinical status of a less rapidly growing malignancy. This projection, of course, must be confirmed by a longer followup. It does, however, demonstrate how these techniques can be used to estimate cure rates within a few years following treatment. Projections of a remission duration curve resulting from a new therapeutic program can be made using an appropriate statistical model based on currently available data. The accuracy of these projections can then be confirmed during more detailed followup.

In conclusion, we can be encouraged by the progress that has been made to date in the treatment of patients with malignant lymphoma. It is now appropriate to discuss "curability," and present data indicate that we may be achieving cure in patients with certain pathologic types, particularly DHL. In other pathologic categories, we must continue our search for new therapeutic agents and attempt to devise more effective treatment programs. Through these efforts we may hope to achieve a significant reduction in tumor burden which eventually will lead to cure for all patients with malignant lymphoma.

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Current Cooperative Clinical Trials in the Non-Hodgkin's Lymphomas[1]

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SUMMARY

Current cooperative group trials in non-Hodgkin's lymphoma have been analyzed for their overall methods and strategies. There has been more frequent application of staging procedures and individualization of protocols for favorable and unfavorable histologies according to the Rappaport classification. Early-stage protocols are evaluating the extent of radiotherapy and the need for chemotherapy as maintenance. In later stages the incorporation of new agents in induction regimens, use of cycle-active agents, development of non-cross-resistant combinations, and use of radiation in bulk disease are being examined. In childhood lymphoma, strategies using both leukemia- or lymphoma-type approaches are being tested. Cooperative group trials should also serve as an extensive repository of data on late effects of treatment and on alterations of the course of the disease for future analysis.

[Cancer Treat Rep 61:1191–1197, 1977]

The current cooperative group trials have widely adopted the Rappaport histologic classification and the requirements for pretherapy staging, and have increasingly incorporated the combined modality approaches in treatment for all stages. Since many of these principles had not been applied in older trials, the new studies are partly based on information from protocols which used less precise methods of classification and staging. Nevertheless, previous group studies provided valuable background data concerning the relative efficacy of various therapeutic regimens and tolerance to them. These are now being tested in a setting of histology and stage-specific protocols.

CHARACTERISTICS OF CURRENT TRIALS

Histologic Classification

In all current studies patients are stratified according to the classification of Rappaport (1). In protocols EST-1475/RTOG-7501, EST-2474, and EST-3474, the ECOG has adopted the concept of different protocols for favorable and unfavorable histologies.[3] Members of the Lymphoma Pathology Reference Center provide a panel to review each institution's material and thus have made possible a uniform classification (2). Mandatory pathologic review by this panel has been accepted and incorporated into most of the current group studies.

Staging Procedures

Non-Hodgkin's lymphoma is staged according to the Ann Arbor classification for Hodgkin's disease (3). The serial staging procedures employed (table 1) depend on the overall intent of the studies (tables 2–4). Bone marrow biopsy and lymphangiography are mandatory for all studies dealing with previously untreated patients. In cooperative group studies it has been difficult to establish clear indications for percutaneous liver biopsy in the face of its inadequacies and to evaluate the application of peritoneoscopy with liver biopsy. Studies restricted

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[3] The following cooperative groups are discussed in this paper: Eastern Cooperative Oncology Group (ECOG, EST), Radiotherapy Oncology Group (RTOG), Southwest Oncology Group (SWOG), European Organization for Research on Treatment of Cancer (EORTC), Southeastern Cancer Study Group (SEG), Cancer and Leukemia Group B (CALGB), and Childrens Cancer Study Group (CCSG).

TABLE 1.—Serial staging procedures: combined modality protocols for stages I–II*

Procedure	EST–1475/ RTOG–7501 (stages I–II)	SWOG–7433 (stages I–II)	EORTC (stages I–II)	SEG–76 NHL–0103 (stages II–III)
Marrow biopsy	+ (2 sites)	+	+	+
Scans	+ (liver-spleen)	–	–	±
Lymphangiogram	+	+	+	±
Percutaneous liver biopsy	+	+	+	±
Peritoneoscopy and liver biopsy	–	–	–	±
Staging laparotomy	+	+	+	±

*+ = required, ± = optional; – = not mentioned.

TABLE 2.—Combined modality protocols: stage I–II non-Hodgkin's lymphoma

Study	Eligibility*	Treatment outline†	
EST–1475/RTOG–7501	Stages I–II including E + EW 1. Favorable histology: NLWD, NLPD, NM, NH	1. a. Segmental field radiation b. Same followed by 6 mos CVP c. Transdiaphragmatic extended field radiation	
	2. Unfavorable histology: DLPD, DM, DH, DU	2. a. Segmental field radiation + 6 mos CVP b. Transdiaphragmatic extended field radiation c. Same + 6 mos CVP d. Total nodal radiation	
EORTC	All histologies, stage I	Mantle *or* inverted Y	1. CVP, 6 mos 2. VCP, 6 mos 3. Observe
	Above diaphragm, stage II	1. Mantle 2. Mantle + abdomen bath	1. CVP 2. VCP
	Below diaphragm, stage II	1. Abdomen bath 2. Abdomen bath + mantle	1. CVP 2. VCP
SWOG–7433	All histologies except DLWD; stages I–II including E	1. Involved field radiation 2. Same followed by CHOP × 6 cycles	
SEG–76 NHL–0103	Only DLPD, DM, NH; stages II–III	Total nodal radiation + abdomen bath	1. COP, 6 mos 2. Observe

*DLPD = diffuse lymphoma poorly differentiated; NLPD = nodular lymphoma poorly differentiated; DLWD = diffuse lymphoma well differentiated; NLWD = nodular lymphoma well differentiated; DM = diffuse lymphoma mixed; NM = nodular lymphoma mixed; NH = nodular histiocytic; DH = diffuse histiocytic; DU = diffuse undifferentiated.

†*See* List of Compounds for definitions of drug combinations.

TABLE 3.—Treatment strategy: stages III–IV non-Hodgkin's lymphoma

Study	Eligibility*	Treatment outline†		
ALGB–7651	Lymphocytic, prior therapy allowed	Vincristine, prednisone, streptonigrin induction, 6 wks		1. CVP maintenance to relapse 2. Involved field radiation consolidation, CVP maintenance
ALGB–7652	Histiocytic, prior therapy allowed	Induction as in ALGB–7651		1. Adriamycin, vincristine, prednisone consolidation, CVP maintenance to relapse 2. Involved field radiation consolidation, CVP maintenance to relapse
EST–2474	Favorable histology (NLWD, DLWD, NLPD, NM, NH), no prior therapy	1. COPP 2. BCVP 3. CP } Induction, 6 mos		1. BCVP maintenance, 13 mos 2. No maintenance
EST–3474	Unfavorable histology (DLPD, DM, DH, DU), no prior therapy	1. BCVP 2. COPA 3. COPB 4. CPOB } Induction, 6 mos		1. BCVP maintenance, 13 mos 2. No maintenance
EORTC	All histologies, no prior therapy	1. CHVP 2. CICS } Induction, 6 mos	Involved field radiation	Consolidation 1. CVP 2. VCP
SWOG–7426/27	All histologies, no prior therapy	1. CHOP-bleomycin 2. CHOP + BCG 3. COP-bleomycin } × 8 repeat × 3; consolidation, 6 mos		1. BCG maintenance, 18 mos 2. No maintenance
SEG–349	All histologies, prior therapy and stage II allowed	1. BCOP 2. COP } Induction, 6 mos		1. BCOP maintenance, 6 mos 2. COP maintenance, 6 mos 3. 2 cycles methotrexate, cytosine arabinoside, 6-thioguanine, 6 mos

*See table 2 for definitions of histologic types.
†See List of Compounds for definitions of drug combinations.

to stages I and II make staging laparotomy mandatory if less invasive methods are not successful in upstaging to stage III or IV disease (EST-1475/RTOG-7501, SWOG-7433, and EORTC stages I–II). Staging laparotomy remains optional in SEG-76 NHL-0103, but the cases are stratified for this option. Laparotomy is indicated in protocols designed for stage III–IV disease only when the clinical situation demands it.

Treatment Strategy in Adults (Tables 2–4)

Radiotherapy and Combined Modality

EST-1475/RTOG-7501 is designed to determine the optimum field size in stage I–II disease; it compares involved with extended field radiation in stage I disease, and extended field with total nodal radiation in stage II. Patients receiving involved field radiation in stage I and extended field radiation in stage II are further randomized to 6 months of maintenance therapy with cyclophosphamide, vincristine, and prednisone (CVP) or observation. In SEG-76 NHL-0103, a similar study in selected histologic types, total lymphoid irradiation is followed by identical maintenance or observation. The EORTC stages I–II protocol compares extended field and total lymphoid irradiation (stage II) followed by comparable maintenance or observation. SWOG-7433 employs radiation fields which are individualized by presentation and its chemotherapy includes adriamycin added to the three-drug maintenance program.

In more advanced disease, radiotherapy plays a secondary role to chemotherapy. Sometimes it is sandwiched between chemotherapy induction and maintenance programs. For example, in the EORTC stages III–IV and the ALGB-7651/7652 studies, involved field radiotherapy is used to sterilize areas of previous bulky disease (so-called iceberg radiation).

Chemotherapy Strategy

The principal objectives of current studies are to define the optimum induction regimens and the

TABLE 4.—Radiotherapy in current studies of non-Hodgkin's lymphomas

Protocol	Stages	Radiation fields	Dose (rads)	Elapsed treatment time (wks)
EST-1475/ RTOG-7501	I, I_E, I_{EW}, II_{EW} (favorable)	Involved and adjacent areas Transdiaphragmatic extended fields	4000–4500	4–8
	I, I_E, II, II_E (unfavorable)	Transdiaphragmatic extended fields Total nodal irradiation	3500–4000 to adjacent areas	
SWOG-7433	I, I_E, II, II_E	Type of presentation determines field 1. Supramediastinal mantle 2. Full mantle 3. Whole abdomen 4. Pelvic field 5. Individualized involved fields	4000 3000 to abdomen	4 4
EORTC	I, II	Mantle, inverted Y, abdomen bath, mantle	4000 2500 to abdomen + 1500 to inverted Y	4 4–6
EORTC	III, IV	Areas of previous bulky disease, "iceberg"	3500–4000	
SEG-76 NHL-0103	II, III	Total nodal radiation and whole abdomen	4000–4500, 3000–3500 to contiguous areas	4–6 for each nodal volume
ALGB-7651/7652	III, IV	Involved areas with 4-cm margin	3000–4000	4–5

type and length of maintenance. In localized disease the program is examining the value of chemotherapy consolidation and maintenance versus observation after the completion of various radiotherapy programs.

In stage III–IV disease the studies focus on the relative value of various induction regimens. CVP forms the backbone of most protocols, but in the induction schemes of various groups the dose schedules of prednisone and cyclophosphamide show considerable variation. Consolidation and maintenance therapy are based on the efficacy of CVP with or without the addition of a nitrosourea (5). A single study (SEG-349), which was based on data from an independent pilot study (6), uses cycle-active agents such as cytosine arabinoside, methotrexate, and 6-mercaptopurine in consolidation.

The basic chemotherapeutic program, including CVP and the subsequent additions of adriamycin, bleomycin (as in CHOP and CHOP-bleomycin), a nitrosourea (as in BCVP), or procarbazine (as in COPP) in various combinations, now offers complete remission in 40%–60% of patients in most histologic types (7–9). Of these, patients with diffuse histiocytic lymphoma are showing prolonged unmaintained complete remissions (10). On the other hand, patients with nodular lymphoma, particularly the poorly differentiated lymphocytic type, follow a pattern of continuous late relapse (11).

Reflecting previous favorable experience with these agents, the induction schemes of ALGB-7651/7652 and the EORTC trial have now added streptonigrin and VM-26 respectively.

Immunotherapy Strategy

SWOG-7426/27, the major group study employing immunotherapy, compares immunotherapy during induction (CHOP + BCG) with two other aggressive combinations (CHOP-bleomycin and COP-bleomycin). Following induction of complete remission, BCG maintenance is compared to observation to determine the value of maintenance immunotherapy (table 3). The remainder of the groups are planning additional studies based on their individual experiences with additional immunostimulant agents.

Treatment Strategy in Children

The non-Hodgkin's lymphomas of childhood are characterized by a high incidence of unfavorable

TABLE 5.—Phase II studies: non-Hodgkin's lymphoma

Protocol	Drug	Dose	Schedule and duration
ALGB-7383	VP-16-213	60–70 mg/m² 90–100 mg/m² 135 mg/m²	Twice weekly iv for 4 wks with maintenance if response
EST-1474	Bleomycin	1 mg sc	Daily for 4 wks with maintenance of 2 mg/wk if response
	VM-26	100 mg/m² iv	Weekly for 4 wks or to relapse; crossover if no response
SWOG-7407	VP-16-213	45 mg/m² iv	Daily by infusion × 5 q3wks
SWOG-7413	*cis*-Dichlorodiammineplatinum(II)	75 mg/m² iv	q3wks
SWOG-7435	Piperazinedione	9–12 mg/m² iv	q3wks
SEG-267	Hexamethylmelamine	280 mg/m² orally	Daily for 6 wks and to relapse

diffuse histology and a generally poor response to conventional "adult" treatment programs (12). Two promising approaches form the basis for current and proposed studies:

a. Application of regimens identical to those employed in childhood acute lymphocytic leukemia (13).

b. Use of combined leukemia and lymphoma treatment schemes with involved field radiation, aggressive induction chemotherapy, central nervous system prophylaxis, and cyclic consolidation-maintenance therapy with several non-cross-resistant pairs of drugs as exemplified by the Memorial Hospital LSA_2L_2 protocol (12).

Both of these approaches show a considerable increase in survival relative to historical controls.

The ALGB-7542 protocol employs leukemia versus lymphoma treatment programs for maintenance following a standard induction therapy which includes both involved field radiotherapy and central nervous system prophylaxis with intrathecal methotrexate. This study is also assessing the value of high-dose methotrexate as consolidation for stage IV disease.

SWOG and CCSG will explore the LSA_2L_2 concept with dose modifications as suggested by pilot studies. The CCSG will compare this concept with a combination program of CVP and systemic and intrathecal methotrexate.

Special Studies

The major group efforts have been addressed to combined treatment with proven agents. A number of other areas may be evaluated in relation to or following these extensive long-term clinical trials.

Phase II studies are an area of major interest. Stratification by histologic type is widely applied. New drugs, mostly used as single agents, are studied in patients refractory to the higher priority combinations. Table 5 lists the current phase II studies.

Hexamethylmelamine and *cis*-dichlorodiammineplatinum(II) have proved active in previous pilot studies, and trials of these agents in combination therapy for non-Hodgkin's lymphoma seem justified (14,15). In one group study (EORTC), VM-26 is now substituted for vincristine in advanced disease.

The cooperative groups also have a special interest and competence in studies of delayed effects of the disease and its treatment. For example, the SWOG has implemented a detailed study of immunologic profiles in patients who have achieved a complete remission on protocol treatment. Similarly, the groups are in an excellent position to contribute knowledge concerning long-term complications of therapy such as secondary malignancies. In fact, the SWOG has demonstrated an increased risk, predominantly of acute leukemia, in patients with Hodgkin's disease receiving both intensive chemotherapy and radiotherapy relative to less intensive use of either modality.[1]

[1]Toland DM, Coltman CA, Jr, and Moon TE. Second malignancies complicating Hodgkin's disease: Southwest Oncology Group experience. N Engl J Med. In press.

TABLE 6.—Summary of therapeutic questions from cooperative group studies

Therapy	Questions
Radiotherapy and combined modality	Optimum extent of radiation fields (stages I and II). Use of maintenance "conventional" chemotherapy after radiation-induced remission. Optimal dose and schedule for "iceberg" radiation (stages III and IV).
Chemotherapy	Optimum induction regimens for favorable and unfavorable types. Optimum maintenance regimens: none, single agents, combinations. Alternating non-cross-resistant combinations. Cycle-active agents in remission. Periodic reinduction and intensification. Activity of new agents.
Immunotherapy	Effect on remission maintenance. Effect on initial response rate and duration.
Special problems	Treatment of childhood non-Hodgkin's lymphoma. CNS prophylaxis.

DISCUSSION

It is apparent from this overview that the cooperative groups are in a position to make significant contributions to our knowledge of the natural history and long-term results of treatment of the non-Hodgkin's lymphomas. Some generalizations may be made concerning the specific objectives of current studies, the problems that may be encountered, and the prospects for future studies.

Table 6 summarizes the questions under study. The major end-points to be determined are survival and response rate. However, before we can interpret the results of these studies, we must establish uniform response criteria. Most lymphoma investigators place the greatest reliance on relapse-free survival and complete remission rate. The use of these two end-points can provide the answer to many questions, but it will take a long time to collect such data.

Of the problems encountered by group studies, one of the most difficult is to tread the narrow line between insistence on complex diagnostic staging and therapeutic procedures which may compromise case accrual, and the kind of uniformity that may sacrifice new ideas and thus alienate the more inquisitive investigators. In fact, early disease studies which require the most extensive deliberations to achieve consensus are those with the greatest accrual problems. To improve accrual we also need to limit the number of questions (or arms) per study, and in the past many group studies have been too ambitious. We also need to achieve uniform criteria for reporting results and more uniformity in data collection so that the studies of various groups can be compared. Our ability to answer questions will then be vastly increased. Stringent criteria are needed, particularly in the assessment of complete remission. Greater comparability of group studies could also be attained by dropping minor variations in induction schemes. A major limitation of phase II studies is the extensive treatment most patients have received before admission to the study.

Despite these many imperfections, the prospects for intergroup cooperation have never been better. In fact, on May 18, 1976, a cooperative discussion group brought together in Bethesda under the auspices of the Cancer Therapy Evaluation Program, Division of Cancer Treatment, NCI, identified the development of common methods of data collection as the first step in collaboration. In the rarer forms of lymphoma (the localized stages and the childhood lymphomas) only intergroup cooperative studies can answer a number of important questions. These studies will therefore determine the optimal intensity and duration of treatment after giving due consideration to toxicity and late effects. The cooperative groups have also served as a registry for these relatively uncommon and complex diseases.

In summary, the diagnosis and treatment of non-Hodgkin's lymphoma have become progressively exciting fields for clinical investigation. The cooperative groups have accepted this challenge and applied increasingly sophisticated techniques to this work. These groups remain our largest resource for defining the value of current concepts and investigating new opportunities in cancer control and treatment.

LIST OF COMPOUNDS

BCOP, BCVP = BCNU, cyclophosphamide, vincristine, and prednisone
CHOP, COPA = cyclophosphamide, vincristine, prednisone, and adriamycin
CHOP-BCG = cyclophosphamide, vincristine, adriamycin, prednisone, and BCG
CHOP-bleomycin = cyclophosphamide, vincristine, adriamycin, prednisone, and bleomycin
CHVP, CICS = cyclophosphamide, adriamycin, VM-26, and prednisone
COP, CVP, VCP = cyclophosphamide, vincristine, and prednisone
COPP = cyclophosphamide, vincristine, procarbazine, and prednisone
CP = cyclophosphamide and prednisone

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Combined Modality Therapy in Malignant Lymphomas [1]

Eli Glatstein,* Sarah S. Donaldson, Saul A. Rosenberg, and Henry S. Kaplan [2,3]

SUMMARY

The treatment of patients with non-Hodgkin's lymphomas remains controversial. The Rappaport classification system has established its clinical value in distinguishing relatively favorable disease (ie, nodular or follicular lymphoma) from relatively unfavorable disease (ie, diffuse lymphoma). Despite the problems of multiple histologies in a given patient posed by the existence of composite lymphomas and by a spectrum of nodularity in a given node, no newer classification has yet proved superior to the Rappaport system. The relative roles of radiotherapy and chemotherapy are reviewed. The primary role of radiation appears to be the control of detectable disease, when adequate doses and volumes are employed. The primary role of chemotherapy appears to be the eradication of microfoci of tumor. Randomized studies of combined modality approaches have produced no definitive evidence of benefit from adjuvant chemotherapy in stage I and II disease of unfavorable histology. The addition of adjuvant radiotherapy in stage III and IV disease of unfavorable histologic types appears to produce some improvement. Aggressive treatment regimens have yet to show any significant advantage over more conservative treatment in patients with favorable histologic types of stage IV extent. This paper emphasizes the need for *expert* hematopathologic interpretation in every study of non-Hodgkin's lymphoma.

[Cancer Treat Rep 61:1199–1207, 1977]

The marked improvement in prognosis among patients with Hodgkin's disease reflects the multimodal approach to treatment, with heavy emphasis on both radiation therapy and effective combination chemotherapy. However, in the non-Hodgkin's lymphomas, the diagnostic evaluation, the optimal treatment, and even the prognosis remain highly controversial. The purpose of this communication is to review the relative roles of radiotherapy and chemotherapy in the treatment of non-Hodgkin's lymphomas of adults and to draw attention to the potential for improvement in the prognosis of these diseases with a multimodal approach.

CLINICAL ASPECTS OF HISTOPATHOLOGIC CLASSIFICATIONS

Confusion about the non-Hodgkin's lymphomas is reflected in the plethora of histopathologic classification systems proposed (1–5). The older classification, "reticulum cell sarcoma, lymphosarcoma, and giant follicular lymphoma," did not prove to be useful and these designations did not appear to represent single disease entities. With the application of the Rappaport system (5), the clinician found a major distinction in prognosis between a nodular or follicular lymphoma (generally indolent) and a diffuse lymphoma (often fulminant). However, even

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this relatively simple system requires *expert* hematopathologic interpretation of node biopsies (6) if valid comparisons are to be made from the literature.

Recent dissatisfaction with the Rappaport system has followed the recognition that many of the large cell lymphomas, termed "histiocytic" by Rappaport on morphologic grounds, have now been shown ultrastructurally and immunologically to be neoplasms made up of large or transformed lymphocytes rather than true histiocytes. Hence, newer classification systems have been proposed based on functional studies (4,7–10). All agree that any classification system should be both scientifically accurate and clinically relevant, yet no one has demonstrated that any of the newer systems have a practical superiority over the Rappaport system. There is little detailed information concerning the clinical value of the newer classification systems, and it remains to be seen whether any of the newer classifications are as reproducible among pathologists or as useful to the clinician as the Rappaport classification.

This paper will not present a critique of the proposed histopathologic classification systems but will discuss certain clinical aspects of lymphoma classification systems. Among patients with non-Hodgkin's lymphomas who have at least two evaluable biopsy specimens of tumor at the time of presentation, the incidence of multiple histologic types is approximately 20% (11). Thus, a significant proportion of patients could be categorized under either of two different headings dependent upon the histology in the specific sample.

Classification of the non-Hodgkin's lymphomas may be further confused when a lymph node biopsy reveals an architecture that is *both* partly nodular and partly diffuse. The Stanford analysis of patients with nodular lymphomas[1] has demonstrated that those who have nodes which contain *both* nodular lymphocytic, poorly differentiated, and diffuse lymphocytic lymphoma, poorly differentiated, have the same favorable prognosis as those who have *only* nodular lymphocytic disease in the node. Likewise, patients with *both* nodular mixed and diffuse mixed lymphoma in the same node have an expected survival and relapse-free survival similar to those whose biopsy shows *only* a nodular mixed pattern. In patients with nodular histiocytic lymphoma, those with both nodular and diffuse architecture appear to have a less favorable prognosis than those whose nodal architecture appears to be entirely nodular. However, this correlation is more difficult to establish because comparatively few patients have nodular histiocytic lymphoma.

Clear distinctions are also obscured when a lymph node shows two separate malignant cell lines in different areas. These "composite" lymphomas pose major problems in classification which can only be clarified in clinicopathologic analysis.

Hereafter in this paper, those patients who have both nodular and diffuse lymphoma in the same node will be referred to as having nodular lymphoma, and those patients categorized as diffuse lymphoma have a diffuse pattern throughout the *entire* node. References utilizing the older classification will be omitted because of the confusion concerning its prognostic implications. The present comments concern adult patients, ie, > 15 years of age, and the staging classification is that of the Ann Arbor system proposed for Hodgkin's disease (12).

ROLE OF RADIATION THERAPY

Although controversies continue concerning the histopathology, accuracy of staging, and predictability among patients with non-Hodgkin's lymphomas, it is clear that high doses of irradiation (ie, > 3500 rads) are often capable of controlling lymphomatous masses permanently (13). If adequate volumes are irradiated with sufficient doses (14,15), a definite cure rate can be obtained in patients with stage I, II (16–21), and even III (14,15,22) disease. Thus, the overall results of radiotherapy must be analyzed not only by dose but also by volume irradiated.

Careful followup of patients receiving radiotherapy after adequate staging has shown that, for stage I and II disease, the most likely initial sites of failure in those who relapsed were lymph nodes that were not irradiated (23). Moreover, this pattern was seen in all the histologic subtypes described by Rappaport. In patients who manifested lymphatic sites of failure, only about half were seen to occur in contiguous nodes. About one third of the patients who failed did so initially in extralymphatic locations, with or without additional detectable lymphatic involvement.

It has been shown that high doses of radiation are highly effective in achieving long-term control in the nodular lymphomas (18). In patients who have diffuse lymphoma, radiotherapy is less effective than in those with nodular disease. Only diffuse histiocytic lymphoma shows a high propensity to recur within the radiation field, but even in diffuse histiocytic lymphoma the majority of sites can be controlled with high-dose radiotherapy.

[1]Warnke RA, Kim H, Fuks Z, et al. The coexistence of nodular and diffuse patterns in nodular non-Hodgkin's lymphomas: significance and clinicopathologic correlation. Submitted for publication.

Because each site of involvement appears independent of the others, results of radiotherapy alone are most striking in stage I disease and decrease with the increase in the numbers of sites at risk (15). However, even in stage III nodular lymphoma (22), high-dose total lymphoid radiotherapy still shows approximately a 33% relapse-free survival at 10 years. Total lymphoid irradiation is less effective in patients with stage III diffuse lymphomas and thus such treatment by itself is usually considered inadequate today.

The work of Johnson et al (24,25) and Chaffey et al (26) has rekindled interest in whole-body irradiation, which has achieved excellent survival in patients with stage III and IV non-Hodgkin's lymphomas. However, long-term survival is entirely consistent with the natural history of patients who have nodular lymphoma and also those who have both nodular and diffuse lymphoma in the same node. Thus, the overall effectiveness of whole-body irradiation is difficult to evaluate without data concerning the relapse-free status of treated patients (22,27) and the provision of a control group for comparison. Moreover, because of the natural history of the nodular lymphomas, these patients should be carefully restaged, including repeat bone-marrow biopsy, before they can truly be assumed to be in complete remission. At present, the precise role of whole-body irradiation remains to be established (28); it appears to have limited curative potential but significant value in palliation. The role of such treatment as an adjuvant to aggressive local treatment for early stages of non-Hodgkin's lymphoma is under investigation (27).

In summary, it is clear that high-dose radiotherapy has curative potential in the early stages of the non-Hodgkin's lymphomas. If such therapy is delivered in adequate volumes, the cure rate can be maximized. In advanced stages (ie, III and IV), however, the likelihood of extranodal spread increases.

It is essential that radiotherapists recognize that the vast majority of patients who have non-Hodgkin's lymphomas have stage III or IV disease. Thus, whereas high-dose irradiation may cure a large number of patients with stage I, II, and even III disease, in the majority of patients with non-Hodgkin's lymphomas radiotherapy will be aimed at controlling large tumors and palliating specific symptoms. The likelihood of ultimate spread beyond the radiation portals remains high.

ROLE OF CHEMOTHERAPY

Historically, non-Hodgkin's lymphomas represent diseases with definite probabilities of response to a wide variety of single chemotherapeutic agents, including corticosteroids, alkylating agents, vinca alkaloids, nitrosoureas, procarbazine, adriamycin, and bleomycin. Multiple-drug chemotherapeutic programs against the non-Hodgkin's lymphomas were developed by combining multiple agents with differing biochemical mechanisms and differing toxicities.

Much of the initial enthusiasm for combination chemotherapy in these diseases was due to high "response rates" because the majority of such patients will manifest a partial or complete remission. However, critical assessments of the value of combination chemotherapy require evidence of improved survival and relapse-free survival after the patient has completed all known treatment (22,27). Despite the excellent response rates for lymphocytic lymphomas treated with cyclophosphamide, vincristine, and prednisone (CVP) (29–33), the relapse rate appears to be linear with time.

In some series the results of combination chemotherapy in diffuse histiocytic lymphoma have proved surprisingly good. Programs such as cyclophosphamide, vincristine, prednisone, and procarbazine (C–MOPP) (34), bleomycin, adriamycin, CCNU, vincristine, and procarbazine (BACOP) (35), and others (36,37) produce complete remissions of prolonged duration in approximately 40% of patients with stage III or IV disease. Moreover, after 2 years of treatment, relapses are exceedingly rare. Thus, combination chemotherapy appears to yield a significant improvement in the prognosis of patients with advanced non-Hodgkin's lymphoma of the diffuse histiocytic type. Paradoxically, there is no clear evidence of long-term disease-free survival (ie, cure) in patients with stage III and IV nodular lymphocytic or nodular mixed disease following combination chemotherapy despite adequate initial control of disease and excellent long-term survival (29–33).

Data are sparse concerning sites of relapse in patients who received chemotherapy alone. However, available data (38) suggest that the most likely sites of failure in such patients are the sites of initial involvement.

COMBINED MODALITY STUDIES

Since the most likely sites of failure following radiotherapy appear to be unirradiated nodes (23) and extranodal sites, and since the most likely sites of failure following chemotherapy appear to be the sites of known involvement (38), it is surprising that few careful prospective studies have been reported using both radiotherapy and chemotherapy in the initial treatment of patients with non-Hodgkin's lymphomas. Undoubtedly the lack of such studies is partly due to controversies concerning

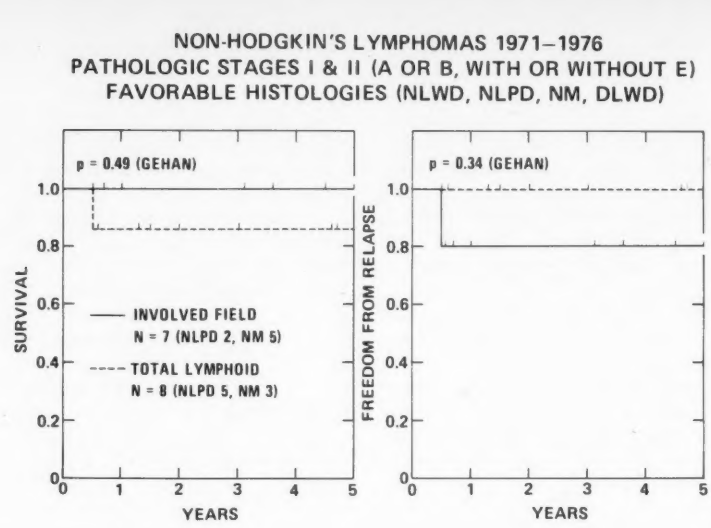
NON-HODGKIN'S LYMPHOMAS 1971–1976
PATHOLOGIC STAGES I & II (A OR B, WITH OR WITHOUT E)
FAVORABLE HISTOLOGIES (NLWD, NLPD, NM, DLWD)
p = 0.49 (GEHAN)
p = 0.34 (GEHAN)
SURVIVAL
FREEDOM FROM RELAPSE
INVOLVED FIELD
N = 7 (NLPD 2, NM 5)
TOTAL LYMPHOID
N = 8 (NLPD 5, NM 3)
YEARS
YEARS

FIGURE 1.—Actuarial survival and relapse-free survival for patients undergoing randomized treatment for pathologic stage I, I_E, II, or II_E non-Hodgkin's lymphomas of favorable histologic types. 1 group of patients received high-dose radiotherapy (≥ 4000 rads) to sites of involvement only; the other group was randomized to total lymphoid irradiation.

definitive staging and histopathologic classification which make prospective randomized studies difficult in the absence of a systematic clinical approach and expert hematopathology (6).

Bonadonna and Monfardini (39) described preliminary results on apparently localized (stage I and II) non-Hodgkin's lymphomas treated with involved-field irradiation with or without six cycles of adjuvant CVP (29). Within the first 2 years, they saw no significant benefit from adjuvant CVP therapy, although it should be noted that most of the lesions in their patients were classified as histiocytic lymphomas.

A series of randomized prospective clinical trials were initiated in July 1971, at Stanford. Details of the rationale, initial evaluation, and preliminary results of treatment have been published elsewhere (40). These trials required biopsy evidence of tumors classified according to the Rappaport system (5). For entry in this study, patients had to be < 65 years of age and have had no previous treatment and no concurrent medical condition thought to impair their ability to withstand extensive diagnostic or therapeutic procedures. In every patient, diagnostic evaluation included routine laboratory studies, bipedal lymphangiography, multiple additional radiographic procedures, and an adequate bone-marrow biopsy. Every patient who did not have overt evidence of stage IV disease following the preliminary workup was subjected to an exploratory laparotomy with multiple lymph node biopsies, splenectomy, liver biopsy, and another bone-marrow biopsy unless he had had exploratory studies before his referral to Stanford.

Figure 1 shows survival and relapse-free survival for patients with favorable histologies (ie, nodular lymphocytic, well differentiated; nodular lymphocytic, poorly differentiated; nodular mixed; and diffuse lymphocytic, well differentiated) (5) who had pathologic stage I and II disease following the extensive workup including laparotomy. Patients were randomized to either involved-field treatment or total lymphoid treatment (midplane doses used were > 3500 rads, usually 4400). Survival at 5 years is excellent; the one death was from an unrelated intercurrent disease. Only one relapse has been detected following the involved-field treatment. Because of the small number of patients who have stage I and II lymphoma of favorable histology and because of the relatively short followup, no conclusions can be drawn at the present time concerning the relative merits of the two treatment approaches.

Figure 2 shows survival and relapse-free survival for patients with pathologic stage I and II non-Hodgkin's lymphomas of unfavorable histologies (nodular histiocytic; diffuse lymphocytic, poorly differentiated; diffuse mixed; diffuse histiocytic; and diffuse undifferentiated). In this study, all patients received total lymphoid irradiation; one half were randomized to six cycles of adjuvant chemotherapy. For patients with diffuse histiocytic lymphoma, the adjuvant chemotherapy was a combination of cyto-

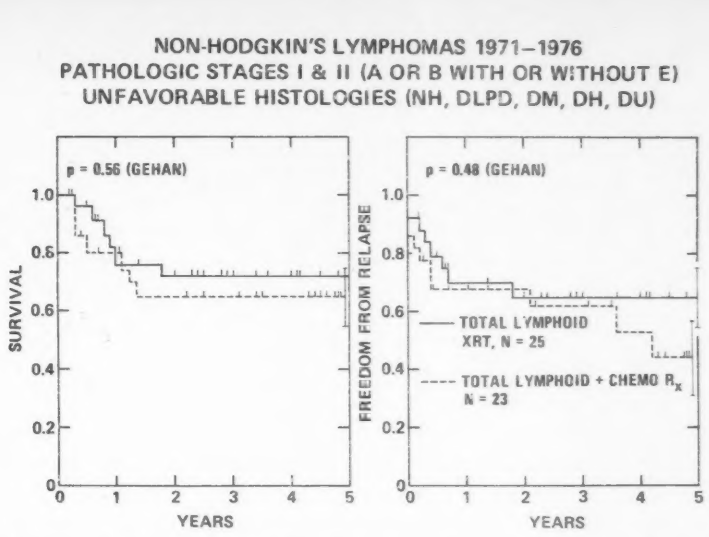

FIGURE 2.—Actuarial survival and relapse-free survival for patients undergoing randomized treatment for pathologic stage I, I_E, II, or II_E non-Hodgkin's lymphomas of unfavorable histologic types. 1 group of patients received high-dose total lymphoid irradiation; the other group was randomized to receive high-dose total lymphoid irradiation + an additional 6 cycles of adjuvant chemotherapy.

sine arabinoside, adriamycin, and 6-thioguanine (CAT) (40), a regimen that achieves a response rate of about 75% in patients with diffuse histiocytic lymphoma. For all other histologies in this study, the adjuvant chemotherapy consisted of CVP (29). After 5 years the survival rate is approximately 70% following total lymphoid irradiation with or without adjuvant chemotherapy. No significant difference is seen between the two groups in relapse-free survival at 5 years. There is a suggestion that the adjuvant chemotherapy employed might be detrimental; however, the control group was a slightly more favorable group of patients, with 11 of the 25 patients classified as stage I compared to only seven of 23 in the combined modality arm. Thus, for local and regional lymphoma of unfavorable histologic types, six cycles of the adjuvant chemotherapies employed have not yet improved survival or relapse-free survival. Moreover, the results of total lymphoid irradiation appear surprisingly good.

Figure 3 shows survival and relapse-free survival for pathologic stage III non-Hodgkin's lymphomas of relatively favorable histologies (nodular lymphocytic, well differentiated; nodular lymphocytic, poorly differentiated; nodular mixed; diffuse lymphocytic, well differentiated; and diffuse lymphocytic, poorly differentiated) (5). All patients received total lymphoid irradiation and one half received six cycles of adjuvant CVP (29) chemotherapy. No significant difference was seen in survival (approximately 65% at 4 years) or in relapse-free survival. The addition of six cycles of CVP has produced no significant improvement.

Figure 4 shows an updated analysis of a randomized study of stage IV non-Hodgkin's lymphomas of favorable histologies (nodular lymphocytic, well differentiated; nodular lymphocytic, poorly differentiated; nodular mixed; and diffuse lymphocytic, well differentiated). Preliminary results of this study have been published elsewhere (30). Virtually all of these patients had bone-marrow involvement with either nodular lymphocytic, poorly differentiated or nodular mixed. Patients were randomized to one of three treatment arms: (*a*) CVP chemotherapy, (*b*) combined modality treatment consisting of two or three cycles of CVP followed by high-dose total lymphoid irradiation followed by additional CVP, or (*c*) single-agent chemotherapy consisting of oral cyclophosphamide or chlorambucil. Survival at 5 years is excellent in all arms, and the most aggressive treatment has produced survival data that are slightly inferior to those of the more conservative regimens. However, as can be seen from figure 4, relapses have continued to occur at a relatively constant rate regardless of the treatment employed. Approximately one third of the patients are still in their initial remission within the first 5 years.

The single-agent data appear excellent but require additional comments. Since the objective of the single-agent arm was not curative, the term "freedom from relapse" for these patients is a

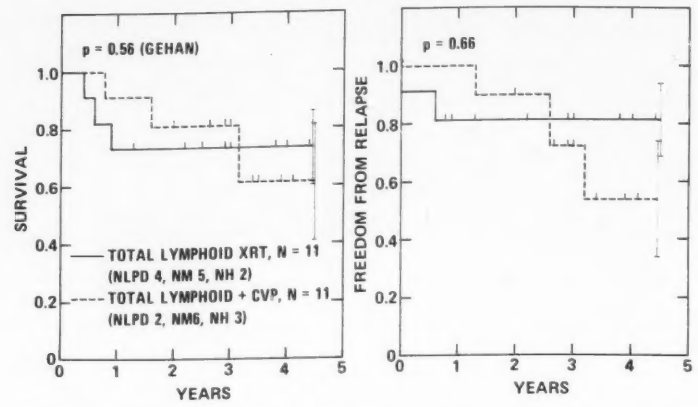
NON-HODGKIN'S LYMPHOMAS 1971–1976
PATHOLOGIC STAGE III (NLWD, NLPD, NM, DLWD, NH, DLPD)
p = 0.56 (GEHAN)
p = 0.66
SURVIVAL
FREEDOM FROM RELAPSE
TOTAL LYMPHOID XRT, N = 11
(NLPD 4, NM 5, NH 2)
TOTAL LYMPHOID + CVP, N = 11
(NLPD 2, NM6, NH 3)
YEARS
YEARS

FIGURE 3.—Actuarial survival and relapse-free survival for patients undergoing randomized treatment for pathologic stage III non-Hodgkin's lymphomas of relatively favorable histologic types. One group of patients received high-dose total lymphoid irradiation; the other group received high-dose total lymphoid irradiation + an additional 6 cycles of adjuvant chemotherapy.

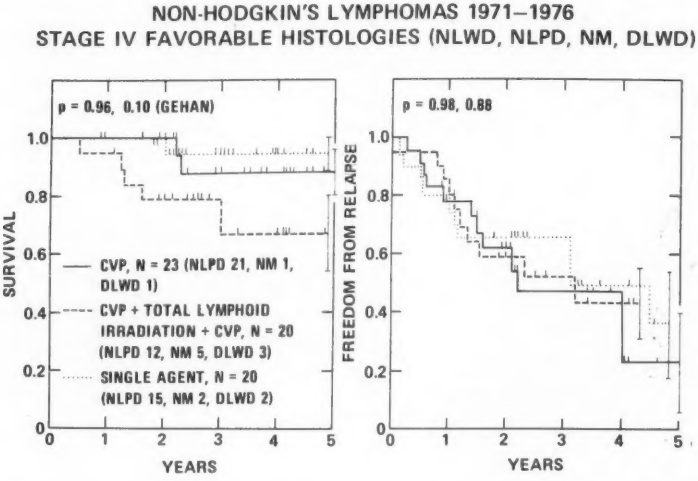
NON-HODGKIN'S LYMPHOMAS 1971–1976
STAGE IV FAVORABLE HISTOLOGIES (NLWD, NLPD, NM, DLWD)
p = 0.96, 0.10 (GEHAN)
p = 0.98, 0.88
SURVIVAL
FREEDOM FROM RELAPSE
CVP, N = 23 (NLPD 21, NM 1,
DLWD 1)
CVP + TOTAL LYMPHOID
IRRADIATION + CVP, N = 20
(NLPD 12, NM 5, DLWD 3)
SINGLE AGENT, N = 20
(NLPD 15, NM 2, DLWD 2)
YEARS
YEARS

FIGURE 4.—Actuarial survival and relapse-free survival (*see* text) for patients undergoing randomized treatment for pathologic stage IV non-Hodgkin's lymphomas of favorable histologic types. 1 group received intensive combination chemotherapy with CVP; the second group was randomized to receive intensive chemotherapy + high-dose total lymphoid irradiation; the third group was randomized to conservative treatment with daily oral chlorambucil or cyclophosphamide only.

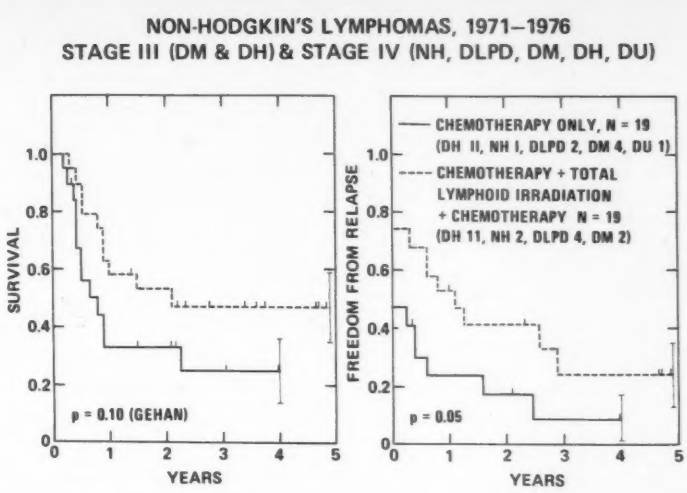
NON-HODGKIN'S LYMPHOMAS, 1971–1976
STAGE III (DM & DH) & STAGE IV (NH, DLPD, DM, DH, DU)
SURVIVAL
FREEDOM FROM RELAPSE
YEARS
YEARS
p = 0.10 (GEHAN)
p = 0.05
CHEMOTHERAPY ONLY, N = 19
(DH 11, NH 1, DLPD 2, DM 4, DU 1)
CHEMOTHERAPY + TOTAL
LYMPHOID IRRADIATION
+ CHEMOTHERAPY N = 19
(DH 11, NH 2, DLPD 4, DM 2)

FIGURE 5.—Actuarial survival and relapse-free survival for patients undergoing randomized treatment for pathologic stage III or IV non-Hodgkin's lymphomas of unfavorable histologic types. 1 group of patients received intensive chemotherapy; the other group was randomized to receive intensive chemotherapy + adjuvant high-dose radiotherapy to total lymphoid fields.

misnomer. In figure 4 the term "relapse-free" applied to patients randomized to single-agent therapy means that the patient continues without a significant change in his or her treatment. Some of these patients are in complete remission, but many are not. If the patient required additional radiation to control a specific area or had to be switched to more aggressive chemotherapy, then he or she was considered a failure. Thus, a patient randomized to single-agent chemotherapy who continues to have stable but detectable disease was not scored as a failure of that arm. The study suggests that the results of aggressive treatment programs for advanced stages of favorable histopathologic types must be compared to those of conservative treatment before ascribing benefits to aggressive programs.

Because the intensive combined modality treatment arm for patients with stage IV disease of favorable histology appeared to be excessive considering the natural history of their disease, we have embarked on a new study which employs whole-body irradiation with local boost therapy instead of the combined modality arm. It is too early to report on this study at the present time, but it may be important to note that of six patients who had bone-marrow involvement at presentation and who received whole-body irradiation to 150 rads and were then subjected to a routine restaging bone-marrow biopsy, three had detectable residual tumor in the marrow, although all six were in complete *clinical* remission before biopsy.

Figure 5 shows a randomized study of patients with non-Hodgkin's lymphomas of advanced stage and unfavorable histologies (stage III: diffuse mixed and diffuse histiocytic; and stage IV: nodular histiocytic, diffuse lymphocytic, poorly differentiated, diffuse mixed, diffuse histiocytic, and diffuse undifferentiated) (5). Patients were randomized between combination chemotherapy only and a combined modality approach consisting of intensive chemotherapy for two or three cycles followed by high-dose total lymphoid irradiation followed by additional chemotherapy. Chemotherapy for patients with diffuse histiocytic and diffuse undifferentiated was CAT (40); for all other histologies in this study it was CVP (29). Of patients who received chemotherapy, 24% survived at 4 years compared to 47% who were alive at 5 years after combined modality treatment. The relapse-free survival data have been generally disappointing, however. Only 9% of the patients randomized to chemotherapy alone continued in their first remission at 4 years. Of the patients who were randomized to the combined modality arm, 24% remained in their first remission at 5 years. These data suggest that the combined modality approach may have a role to play in advanced stages of non-Hodgkin's lymphomas of unfavorable histologies.

FUTURE DIRECTIONS

The studies that have been published must be interpreted carefully and cautiously. *Expert* inter-

pretation of histology is essential in any study (6,11) of non-Hodgkin's lymphomas. For patients who have relatively favorable histologies, probably 10 years must elapse before any conclusions can be drawn.

In looking at the results of high-dose total lymphoid irradiation for stage I and II disease of unfavorable histology (fig 2), radiotherapists should recognize that improvement in these results must come from better programs of chemotherapy or perhaps some newer techniques of immunotherapy, since the volume irradiated has already become enormous. Similarly, chemotherapists must recognize that combination chemotherapy gives results in patients with non-Hodgkin's lymphomas that are generally inferior to those achieved in Hodgkin's disease. All concerned must have a full appreciation of the morbidity associated with both modalities if the treatments are to be tailored to the anticipated prognosis of each histopathologic type.

The primary value of conventional radiotherapy is the control of bulky detectable disease. The primary value of chemotherapy appears to be the eradication of microscopic foci of disease. The crucial problem remains how to integrate these two modalities to maximize the benefits of both.

It is not clear at present how much chemotherapy is appropriate as an adjuvant to radiotherapy in these patients; similarly, it is not clear what dose of radiation is required as an adjuvant to chemotherapy. Moreover, there is an urgent need to study other chemotherapeutic regimens in similar, well-controlled prospective clinical trials.

We are presently reducing the dose of irradiation in patients with advanced stages of unfavorable histologies to 3000 rads instead of 4400 rads and alternating two cycles of combination chemotherapy with separate periods of radiation to mantle (or "mini-mantle," a supramediastinal field) upper abdominal and pelvic fields. Such an alternating sequence of two treatment modalities requires much closer co-operation between the various specialists than is usually expected. Only such close co-operation between chemotherapists and radiotherapists offers hope for significant improvement in the results of treatment for patients with non-Hodgkin's lymphomas.

LIST OF COMPOUNDS

Actinomycin D: NSC–3053

Bleomycin: NSC–125066; CAS reg. No. 11056–06–7; [2,4′-bithiazole]-4-carboxylic acid, 2′-(2-aminoethyl)-, monohydrate

CCNU: NSC–79037; CAS reg. No. 13010–47–4; urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-

Chlorambucil: NSC–3088; CAS reg. No. 305–03–3; butyric acid, 4-[*p*-[bis(2-chloroethyl)amino]phenyl]-

Cyclophosphamide: NSC–26271; CAS reg. No. 6055–19–2; 2*H*–1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate

Cytosine arabinoside: NSC–63878; CAS reg. No. 69–74–9; cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride

Prednisone: NSC–10023; CAS reg. No. 53–03–2; pregna-1, 4-diene-3,11,20-trione, 17,21-dihydroxy-

Procarbazine: NSC–77213; CAS reg. No. 491–88–3; *p*-toluamide, *N*-isopropyl-α-(2-methylhydrazino)-, monohydrochloride

6-Thioguanine: NSC–752; CAS reg. No. 1832–72–0; purine-6-thiol, 2-amino-

Vincristine: NSC–67574; CAS reg. No. 2068–78–2; leurocristine, sulfate (1:1)

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New Approaches to the Treatment of Non-Hodgkin's Lymphoma[1]

Emil Frei III,* Stuart Schlossman, and Mervyn Israel[2]

There are a large number of effective agents for the treatment of non-Hodgkin's lymphoma (NHL) (table 1). These agents are being combined in varying dose schedules and combinations in an effort to increase the complete remission rate and duration of survival. It may be anticipated that the construction of improved combination programs will result from increasing pharmacologic, cytokinetic, and tumor biologic information, as well as the development of improved experimental models.

Preliminary studies have indicated that the methotrexate (MTX)-citrovorum factor (CF) rescue program is effective in patients with NHL (1,2).[3] Pitman et al (2) have demonstrated that, by appropriate attention to urine volume flow and alkalinization, very large doses of MTX (from 0.5 to 7 g/m^2) can be delivered with CF rescue at 24 hours with safety. With 0.5 g/m^2 of MTX, plasma concentrations of 10^{-5} M and spinal fluid concentrations of 10^{-6} M can be reached, and with doses ranging up to 7 g/m^2, plasma concentrations of 10^{-4} M and spinal fluid concentrations of 10^{-5} M can be achieved (fig 1) (3).[4] Such programs are therapeutic for overt meningeal leukemia and lymphoma and there is preliminary evidence that they provide "prophylaxis" for meningeal leukemia in patients with acute lymphatic leukemia (4). This program delivered on a weekly basis has produced objective responses in seven of nine patients with NHL.[5] It addresses several of the major obstacles to successful treatment with other current regimens.

One cause of treatment failure is inadequate tumor cytoreduction by intermittent intensive combination chemotherapy. Since the MTX-CF program is non-myelosuppressive, it can be combined at full doses with other agents, and in accordance with established principles of combination chemotherapy, this should afford an additive tumor cytoreductive effect. A second obstacle to successful treatment with intermittent combination chemotherapy is that recrudescent tumor may occur between courses due to the rapid proliferative thrust. Again, because the MTX-CF program is non-myelosuppressive, its safe interposition between courses of treatment is possible. Finally, an increasing cause of treatment failure is the development of meningeal lymphoma in patients who otherwise are in complete remission (5). As above, this program has the potential of providing effective prophylaxis for this complication.

TABLE 1.—Response rate of NHL to single drugs

Drugs	Lymphocytic (%)	Histiocytic (%)
Prednisone	60–80	20–30
Mechlorethamine	50–70	40–50
Cyclophosphamide	50–70	50–70
Chlorambucil	40–60	20–30
Procarbazine	40–50	20–35
Vinblastine	15–25	20–35
Vincristine	40–65	40–80
VM-26	50–60	30–35
VP-16-213	25–30	10–15
Adriamycin	35–50	50–65
Bleomycin	30–40	30–40
BCNU, CCNU, methyl-CCNU	20–30	25–35
Streptozotocin	20–30	10
DTIC	20–25	10
MTX	15–25	15–25
Cytosine arabinoside	20–25	15–20

Adriamycin[6] combined with vincristine and prednisone is a highly effective program for NHL, and indeed is as effective as any other program involving cyclophosphamide (6). Thus, one approach to improving therapy for NHL would be to develop a better adriamycin analog. A semisynthetic analog synthesis program was initiated 3 years ago by Israel and Modest. They wished to modify the adriamycin molecule in three ways. First, adriamycin differs from daunorubicin only in that it has a hydroxyl on the carbon 14 in place of a hydrogen (fig 2). This modification renders adriamycin much more effective at the optimal dose in most transplanted tumor systems and probably in man. Ac-

[1] Supported by Public Health Service grant CA-19892 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

[2] Sidney Farber Cancer Institute, Boston, Mass.

[3] Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl}-.

Citrovorum factor: NSC-3590; CAS reg. No. 6055-86-5; glutamic acid, *N*-[*p*-[[(2-amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxy-6-pteridinyl)methyl]amino]benzoyl}-, calcium salt.

[4] Ensminger B, Parker L, et al. Personal communication.

[5] Canellos G, Pitman S, and Skarin A. Personal communication.

**Reprint requests to:* Dr. Emil Frei III, Sidney Farber Cancer Institute, 44 Binney St, Boston, Mass 02115.

[6] Adriamycin: NSC-123127; CAS reg. No. 23214-92-8.

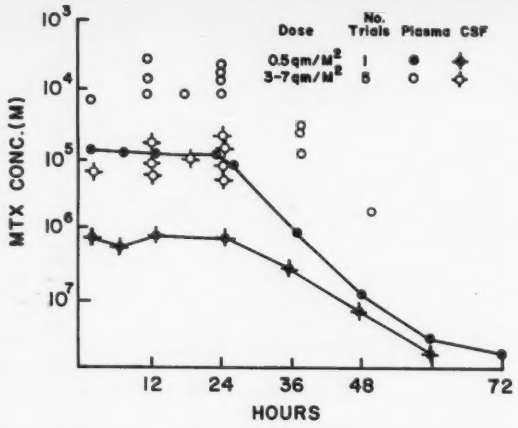

FIGURE 1.—MTX-CF rescue program. Plasma and cerebrospinal fluid MTX levels during and after a 24-hr iv infusion.

cordingly, systemically varied substituents on the carbon 14 were introduced. The amino group on the amino sugar provides the major polarity and water solubility of adriamycin. Since adriamycin is actively transported into cells, and since drug-induced resistant cells have poor transport systems (7), Israel decided to modify the amino group in the direction of increasing lipid solubility and, therefore, passive transport into cells (8).

From physiochemical, biochemical, and X-ray defraction studies, it has been determined that adriamycin binds to DNA (9). The flat tetracycline moiety of the molecule is intercalated between nucleotides. The amino group is external and perhaps complexes with the phosphate group of the phosphodiester exoskeleton of DNA. The major biochemical effect of adriamycin is on DNA replication and transcription, and results from this intercalation. This is another reason for modifying the amino group on the amino sugar.

After synthesizing almost 200 compounds and comparing them in various systems, a di-substituted compound (AD 32) with a valerate in the 14 position and a trifluoro-acetyl on the amino group was found to have the best therapeutic index (8). Preliminary biochemical studies to date in the rodent and rabbit indicate that adriamycin is, at the most, a trace metabolite of AD 32, and thus AD 32 is not a simple "repository form of adriamycin."[7] When AD 32 is compared to adriamycin across a dose range in two important lymphoblastic lymphomas, the L1210 and the P388 in the mouse, AD 32 (at the optimal dose) not only markedly increases the life-span but is also "curative" (table 2) (8,10). Adriamycin and AD 32 are highly fluorescent and have been studied in vitro in cells in culture by Krishan (*see* left side of fig 3). Adriamycin concentrates almost exclusively in the nucleus of cells. AD 32 uptake is more rapid and the drug concentrates in the cytoplasm (11).

Thus, AD 32 is substantially more lipid soluble, has a different intracellular distribution, and binds substantially less readily to DNA than does adriamycin. At the least, it is very different from adriamycin in terms of physiologic and cellular pharmacology, and may possibly have a fundamentally different mechanism of action. Preliminary studies in the rat and rabbit indicate that AD 32 may be

[7] Israel M, and Wilkinson J. Personal communication.

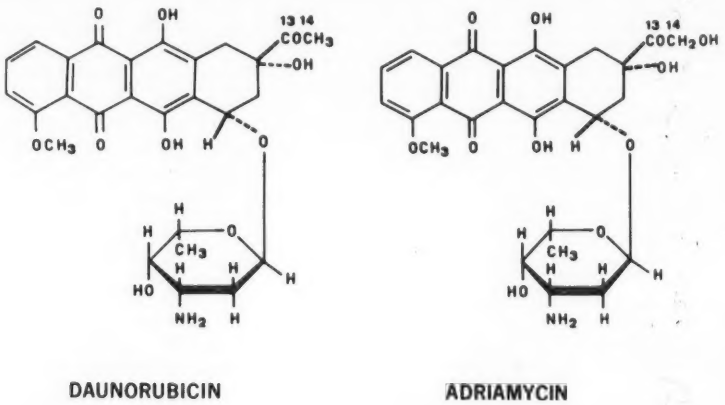

FIGURE 2.—Structural formulas of the anthracyclines, daunorubicin and adriamycin.

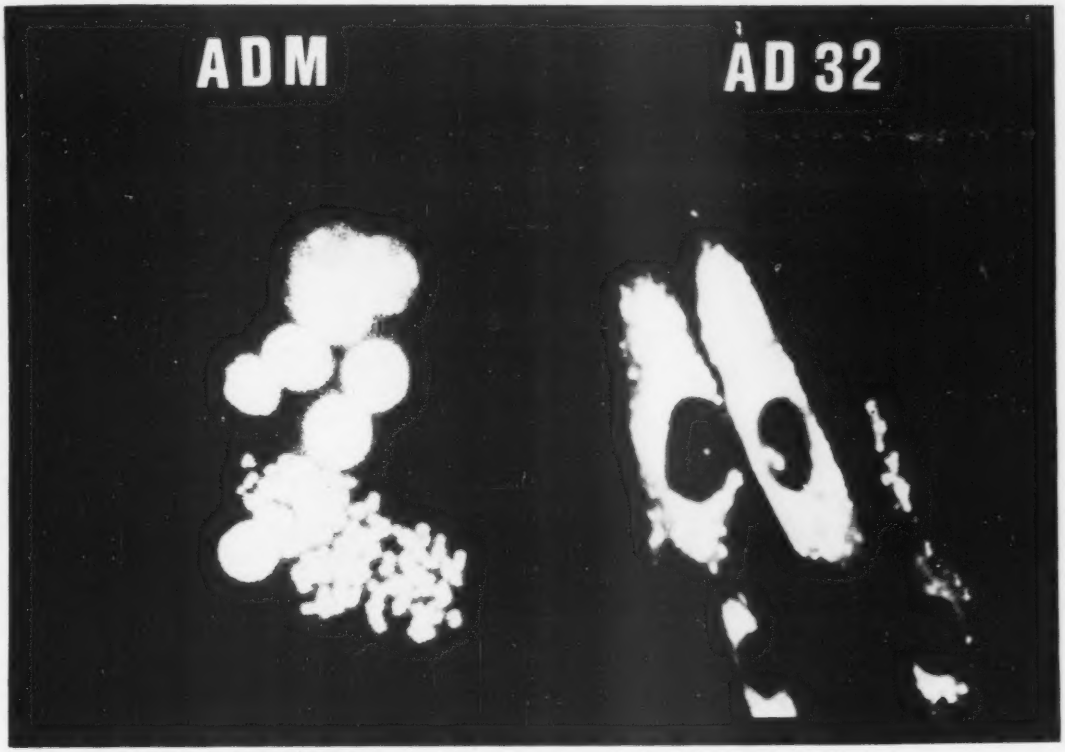

FIGURE 3.—Fluorescent analysis of cells exposed to adriamycin (ADM) and AD 32 in vitro. ADM is taken up slowly and fluorescence is concentrated in the nucleus. Uptake for AD 32 is rapid and fluorescence is primarily in the cytoplasm.

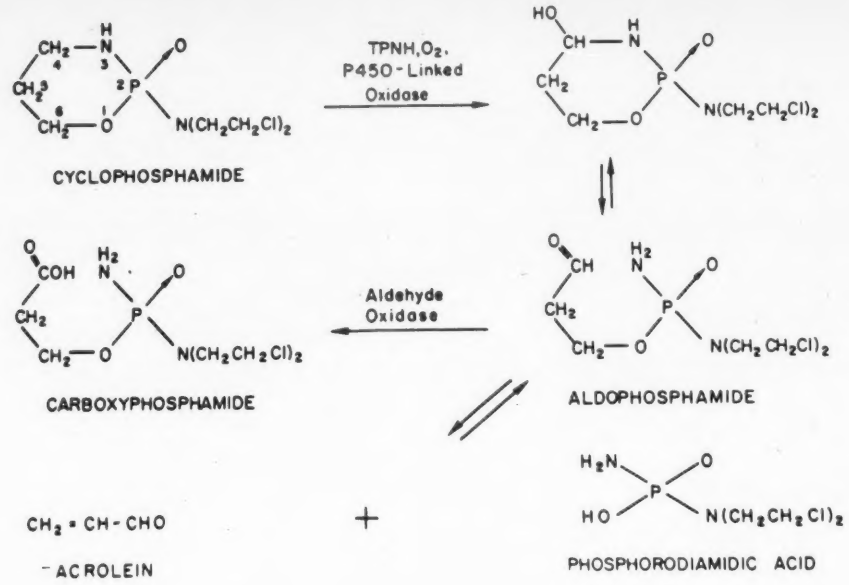

FIGURE 4.—Biotransformation of cyclophosphamide.

less cardiotoxic than adriamycin. It is currently being prepared for clinical trial.

Another important agent in the treatment of NHL is cyclophosphamide* (fig 4). It is activated by microsomal enzymes. The ring is cleaved to aldophosphamide and there is good evidence that it enters the cells in this form where it may be inactivated to carboxyphosphamide or converted to phosphorodiamidic acid, which is an active alkylating agent. Analogs of phosphorodiamidic acid have been made; most particularly, aldophosphamide has recently been synthesized and this compound, along with its analogs, represents a promising area of therapeutic research for lymphoma.

I would like to turn now to the therapeutic implication for lymphoma of tumor immunology. A polyacrylamide gel preparation of HL-A and HL-A-related antigens obtained from a B lymphocyte in culture is presented in figure 5. Column A contains a purified fraction of six glycoproteins. The fractions in column D are clearly related to HL-A or microglobulin cell-surface antigens. Based on rodent studies of the H2 locus, it was suspected that the 23,000 and 30,000 molecular weight species (column C) might be similar to the Ia-antigen system (12). Accordingly, heterologous antibodies to these were prepared in the rabbit, and such antibodies, appropriately absorbed and labeled with fluorescein, were studied for reactivity against various cells. These analyses were performed using the fluorescence-activated cell sorter (fig 6) (13). This may be considered a third-generation instrument complex (the Coulter counter and the cytofluorograph being the first and second generations, respectively). In this system, individual cells are placed in droplets by ultrasound. For the present study, an incident laser beam strikes the individual cells. Those which have fluorescent-labeled antibodies attached were recognized by a photomultiplier system. This triggered an electrical field which deviated the labeled cells such that they could be collected, that is, sorted separately from the unlabeled cells. Thus, cells can be enumerated, processed, and sorted at the rate of 40,000/second. It is a much more rapid and a substantially more sensitive and quantitative way of detecting immunofluorescence as compared to fluorescence microscopy. The results are expressed schematically in figure 7. The Y-axis indicates the number of cells and the X-axis the magnitude of fluorescence. One can set the "gate" at any point and sort, for example, only highly labeled cells. The above antibody, that is, anti-P2330, labeled all B cells, but did not label T cells (figs 8 and 9) (14).

Schlossman prepared another antibody to purified acute lymphatic leukemic cells from a patient (BK) who was thought to have T cell leukemia. The purified cell preparation was injected into rabbits.

*Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate.

TABLE 2.—Comparative survival data for adriamycin and AD 32 vs murine P388 and L1210 leukemias (BDF, male mice: treatment ip each day, Days 1–4)*

Agent	P388 leukemia†				L1210 leukemia§			
	Optimal dose (mg/kg)	ILS (%)	No. of survivors/No. of mice treated		Optimal dose (mg/kg)	ILS (%)	No. of survivors/No. of mice treated	
			30-day	60-day			30-day	60-day
Adriamycin	4.0	+132	0/6		4.0	+50	0/7	
AD 32	40.0	+429	4/5	3/5	50.0–60.0	> +445‡	6/7	6/7

*Reproduced with permission from ref 10.
†10^6 tumor cell inoculum ip.
‡Calculated as of Day 60; cumulative experience: > 70% cure rate.
§10^5 tumor cell inoculum ip.

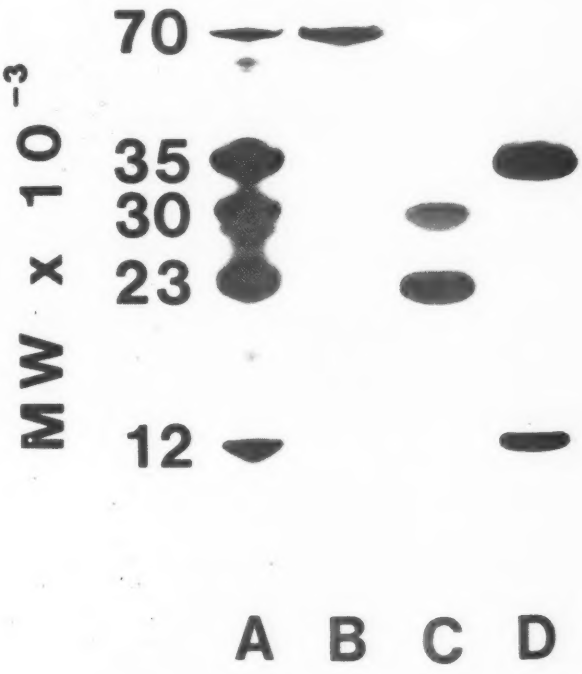

FIGURE 5.—Polyacrylamide gel analysis of partially purified HL-A and related antigens. Column A contains 6 glycoproteins; the fractions in column D are related to HL-A or microglobulin cell-surface antigens; column C, based on extrapolation from rodent H2 studies, presumably represents Ia antigens (12).

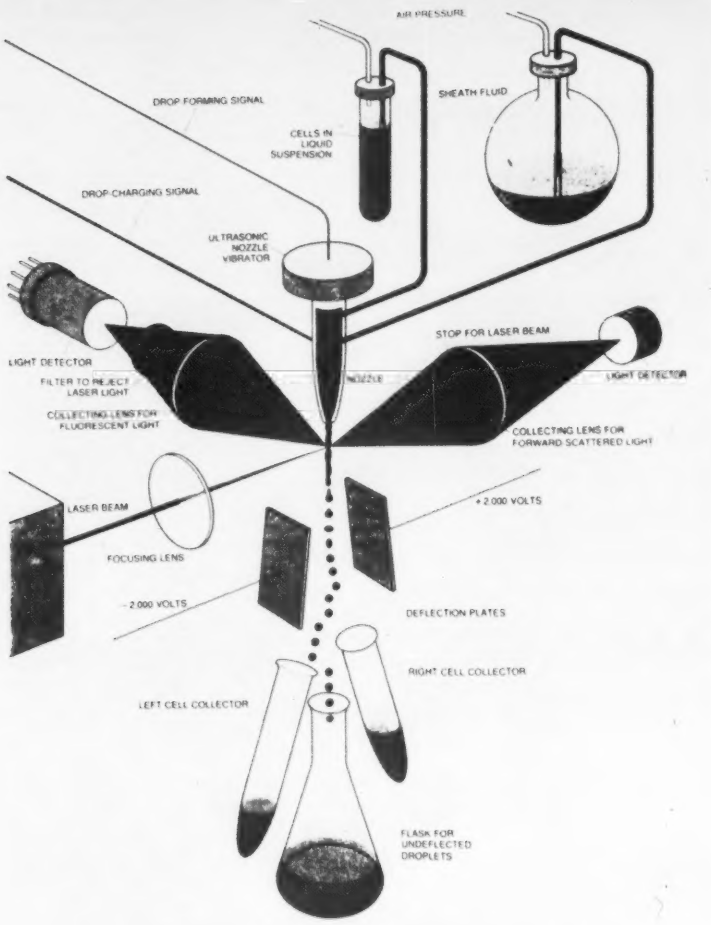

FIGURE 6.—Fluorescence-activated cell sorter (schematic diagram).

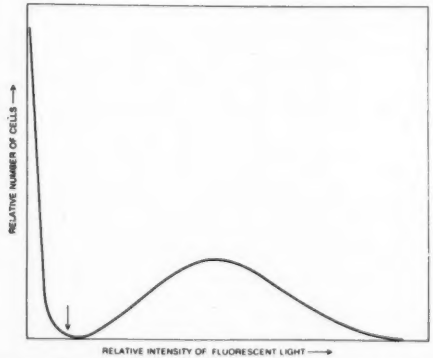

FIGURE 7.—Sample read-out from the fluorescence-activated cell sorter. Y-axis involves the relative No. of cells and X-axis involves the cohort of cells labeled with fluorescent-labeled antibody and the magnitude of labeling.

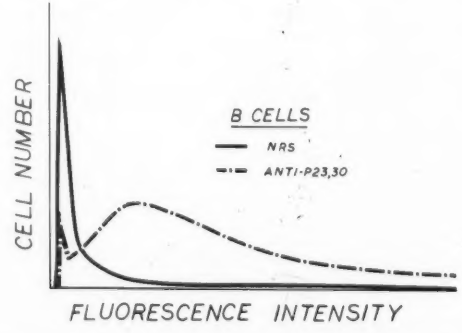

FIGURE 8.—Fluorescence-activated cell sorting of normal peripheral blood B cells.

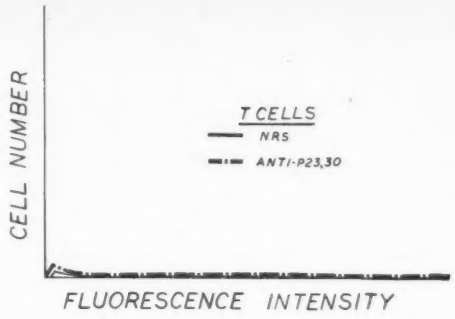

FIGURE 9.—Fluorescence-activated cell sorting of normal peripheral blood T cells.

The immunoglobulins were harvested and absorbed with purified normal B cells obtained when the patient was in remission. This antibody reacted with the patient's leukemic cells, whereas the P2330 antibody did not (fig 10) (14).

A breakdown of the reactivity of these two antibodies is presented in table 3. P2330 reacts with all normal B cells and null cells, but not with T cells. It does not react with normal thymocytes, peripheral blood, or bone marrow cells. It reacts with the blast cells of 75% of acute lymphoblastic leukemia (ALL) patients. This suggests but does not prove that most ALL is, in fact, B cell lymphocyte-derived. In contrast, anti-BK antibody does not react with normal B cells, and importantly, does not react with normal circulating T cells. It does react with a subset of lymphocytes in the thymus. It does not react with the normal marrow. It does react with the blast cells of the 20%–25% of patients who are not reactive to P2330 (14). These patients usually have other clinical and laboratory evidence of T cell disease.

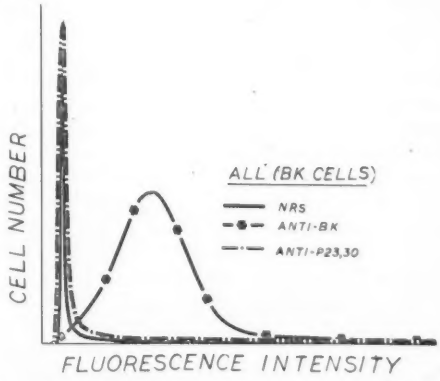

FIGURE 10.—Fluorescence-activated cell sorting of peripheral blood leukemic cells from a patient (BK) with ALL and a mediastinal mass.

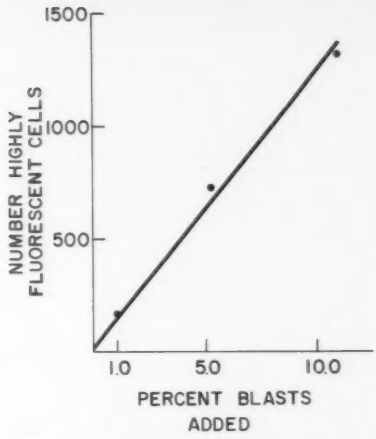

FIGURE 11.—Recovery of leukemic T cells mixed with normal bone marrow cells using anti-BK antibody and the fluorescence-activated cell sorter. Y-axis is % of leukemic T cells admixed with normal marrow.

A major treatment problem and obstacle to cure in leukemia and lymphoma is our inability to detect and measure minimal disease. Once a patient enters complete remission, we are "flying blind" and need "instruments" to apply curative treatment. The above techniques offer an approach to this problem (fig 11). In mixing experiments involving anti-BK antibody positive leukemic cells and normal marrow, one can readily enumerate and sort (recover) the leukemic cells. This can also be accomplished with a 5%, 1%, and provisionally 0.1% leukemic cell-normal bone marrow mixture. This is better by at least one order of magnitude than optical microscopy and can be improved. It is applicable not only to the bone marrow of patients with leukemia and lymphoma, but potentially to the lymph nodes of patients with lymphoma. The development of the above and additional antibodies specific or nearly specific for neoplastic monoclonal disease, plus such instrumentation, provides increasing opportunity for such measurements. The duration of treatment and the quality of treatment once patients have achieved complete remission would be enormously and rationally influenced by knowing the presence and vector of minimal disease. Indeed, all of the elegant but very complex clinical experimental designs which have been presented at this symposium would be radically influenced by such an "instrument" or marker.[9]

[9]Chess L, Sallan S, and Schlossman S. Personal communication.

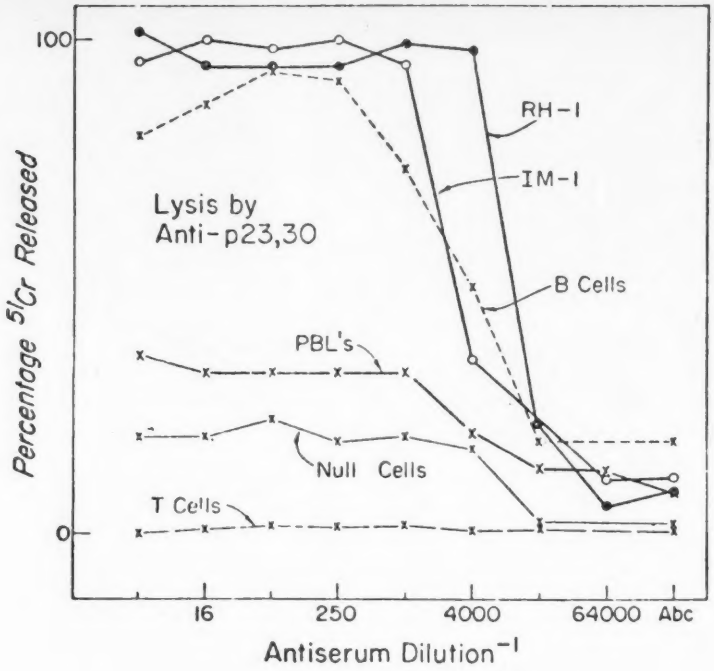

FIGURE 12.—Cytotoxicity in vitro of anti-P2330. RH-1 and IM-1 are established human B lymphocytes in culture. PBL = peripheral blood lymphocytes.

TABLE 3.—Reactivity of anti-HTL (anti-BK) with normal, leukemic, and related tissues

Cell source	Antisera	
	Anti-HTL (anti-BK)	Anti-P2330
Fetal thymocytes	3/3	NT*
Thymocytes	3/3	0/3
Peripheral T cells	0/32	0/32
Peripheral B cells	0/32	32/32
Peripheral null cells	0/10	15/15
Normal marrow	0/5	0/5
Acute lymphatic leukemia	10/56	40/56
Chronic lymphatic leukemia	0/7	7/7
Acute myelogenous leukemia	0/15	12/14
Chronic myelogenous leukemia	0/3	0/3
Total		10/56

*NT = not tested.

In addition to measuring minimal residual disease, this approach should assist in studying the pathogenesis and prognostic variables of lymphoma. In ALL the type of lymphocyte rendered neoplastic may markedly influence prognosis. For example, in a study of 110 patients with ALL treated over the past 3 years, Sallan et al (15) at this institute have demonstrated that 85 of 90 patients with non-T cell leukemia continue in complete remission whereas only 13 of 20 patients with T cell disease have done so ($P = < 0.05$). There is evidence in experimental animals that B cell leukemia such as L1210 responds substantially differently than T cell leukemia such as AKR to agents known to be effective in lymphocytic leukemia and lymphoma in man (table 4). Because these data derive from a number of studies (16), I have semi-quantitatively ranked them from 10 (maximum activity) to 0 (no activity). There are very substantial differences: in particular, the antimetabolites, MTX and 6-mercaptopurine, while quite active in B cell leukemia, are essentially inactive in the T cell leukemia. Because of this and because of the failure of our current program in T cell leukemia in man (in contrast to its great effectiveness in non-T cell leukemia), we have modified our treatment program for T cell leukemia giving greater emphasis to cyclophosphamide, adriamycin, and cytosine arabinoside. The general point to be made is that through immunopathology studies a better understanding and a

TABLE 4.—Effect of antitumor agents on experimental B and T cell leukemias*

Drug	Mouse leukemia	
	AKR (T cell)	L1210 (B cell)
Cyclophosphamide	10	6
Adriamycin	4	8
Cytosine arabinoside	6	6
Vincristine	4	4
MTX	1	5
6-Mercaptopurine	0	3
Prednisone	1	0
L-Asparaginase	0	0

*Antitumor activity scale, 10 (maximum activity) to 0 (no activity).

more rational classification of human NHL are possible and we must accordingly use experimental models that incorporate and apply this understanding.

Finally, studies such as the above have therapeutic implications. Not only do these antibodies bind with great specificity to the tumor cells, but they are potently cytotoxic in the presence of complement (fig 12). B cells, in vitro, are destroyed by dilutions to 1:4000 of anti-P2330, whereas T cells are not affected. An antibody such as the anti-BK, where reactivity for normal cells is limited to a subset of thymocytes and which affects "malignant" but not normal T cells or other normal cells, would provide a measure of specificity that exceeds that of chemotherapeutic agents. The same is true though somewhat less so for the anti-P2330. The implications of the above are currently being studied in in vivo experimental tumor systems.

In conclusion, we have listed only highly selected approaches to the improvement of the treatment of NHL through chemotherapy, immunoevaluation, and immunotherapy. Time precludes covering the numerous experimental studies in related areas that show potential for clinical trial in the reasonably near future. Twenty-five years ago, a few radiotherapists pioneered the curative treatment of localized lymphoma, and 12 years ago a few chemotherapists did the same for disseminated lymphoma. We still have a long way to go in NHL. The clinical and scientific base, leads, and resources have increased enormously. Continued progress in the understanding and definitive treatment of NHL is assured.

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DISCUSSION V: Overview of the Non-Hodgkin's Lymphomas [1,*]

Dr. Levy: Dr. Frei, how do you propose to monitor subclinical disease in the marrow of patients with leukemia using an antiserum which recognizes normal B-cells?

Dr. Frei: The T-cell was employed in the marrow-mixing experiments and gave a high degree of reproducibility. My intention was to present it as a prototype rather than the final answer. Dr. Greis and a number of other workers have prepared antibodies with various degrees of specificity. This area is developing rapidly and it remains to be seen whether these two antibodies will be reliable monitors. In any event, anti-B antibody is obviously not good for lymph nodes.

Dr. Royston: Dr. Frei, have you any comments concerning the terminal transferase data in acute lymphocytic leukemia? Some data seem to suggest that 90% of the cells may be of thymic origin, but the anti-P2330 data suggest that they may be of B-cell origin.

Dr. Frei: That is a discordancy which we really don't understand. We had thought that the terminal transferase was T-cell determined and that conclusion is not consistent with our antibody data.

Dr. Royston: Have you looked for the P2330 antigen in any of the T-cell leukemia cell lines that are in culture?

Dr. Frei: Yes. They are positive.

Dr. Seligmann: May I comment on some of Dr. Frei's data and upon your question? I agree that some antisera may be useful in detecting small numbers of residual malignant cells. I didn't discuss this matter because at present this approach applies more to leukemia than to the lymphomas. A good example is the specific antibody for non-T, non-B blast cells, especially that of Dr. Greis. The anti-IA antiserum P2330 is not a good example because it destroys B-cells. Secondly, you should not conclude that acute lymphocytic leukemia cells without T-markers are B-cell in origin as you do. The transferase data may be more important than the IA data. I believe I am correct in saying that anti-IA P2330 antiserum also labels acute myeloblastic leukemia cells which cannot be B-cells. Am I correct? Does your anti-IA and other anti-IA antibody also label acute myeloblastic leukemia cells?

Dr. Frei: Yes. Anti-P2330 does label acute myeloblastic leukemic cells, but does *not* label normal myeloblastic cells or any normal marrow cells. It is difficult to accept that myeloblastic cells are B-cell derived; a much better explanation is that P2330 is a differentiation antigen.

Dr. Seligmann: I agree. That is why I would not call these non-T, non-B acute lymphocytic leukemia cells, B-derived acute lymphocytic leukemia. We have no hard data.

Dr. Sullivan: From 1968 to 1974 we treated children with diffuse histiocytic lymphoma with CVP on a somewhat different schedule than that used in adults, and achieved a 50% cure rate.[2] Some of these cured children (we believe they are cured) have developed serious problems with the urinary bladder. One child developed fibrosis and, if it were not impossible, should have had a urinary diversion. A very large number of adults have received CVP in some type of schedule; have any had bladder problems?

Dr. DeVita: In our hands CVP has produced relatively little bladder toxicity, especially if the patient is properly coached to consume a lot of water. Does anybody else wish to comment on bladder problems with CVP?

Dr. Bloomfield: We have been seeing increasing problems, especially in adults over the age of 60, when we use both CVP and cyclophosphamide. We have had to remove a number of bladders because of uncontrollable bleeding.

Dr. DeVita: We have not had that kind of difficulty even with high single doses of cyclophosphamide.

Dr. Muggia: Dr. Sullivan, did those children receive radiation therapy to the bladder area? As you know, chemical and radiation toxicity are probably synergistic.

Audience: Dr. Seligmann, in your talk did you say that one cannot find a monoclonal staining pattern

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[1] The following investigators participated in this discussion: *V. T. DeVita* (chairman) and *F. M. Muggia* (National Cancer Institute, Bethesda, Md); *Dr. Levy, I. Royston, E. Glatstein,* and *S. A. Rosenberg* (Stanford University School of Medicine, Calif); *E. Frei III* (Sidney Farber Cancer Institute, Boston, Mass); *M. P. Sullivan* (The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston); *M. Seligmann* (Hôpital Saint-Louis, Paris, France); *C. D. Bloomfield* (University of Minnesota, Minneapolis); *J. Klein* (Lombard Medical Group Inc, Thousand Oaks, Calif); *W. Rick* (Los Angeles, Calif); *L. Grossman* (Vancouver, Canada); and *F. Gibbs* (University of Utah, Salt Lake City).

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[2] CVP = cyclophosphamide, vincristine, and prednisone.

except through the production of that product by those cells? Would you elaborate on that?

Dr. Seligmann: When you prove that an immunoglobulin is monoclonal, you have established that it is produced by the cell; however, to prove it you should be able to demonstrate that all the molecules in all the cells have not only the same type and class of light and heavy chains but also the same variable regions, idiotypes, antibody activity, and so on. You may have an antibody to leukemia-associated membrane determinants on the membrane of leukemic cells, because some of these antibodies are homogeneous (as are many antibodies) and may contain only gamma and kappa chains, for instance. When you prove monoclonality by all the necessary criteria it's fine, but if you just show one type of light chain and one type of heavy chain, it may be highly misleading.

Dr. Klein: Dr. DeVita, which patients and which histologic types are the best candidates for maintenance chemotherapy? Will you also elaborate further on current studies on immunotherapy?

Dr. DeVita: To date we have no good evidence that maintenance is of any value in diffuse histiocytic lymphomas. The programs that employ some form of maintenance are really using continued induction treatment. Some workers make a distinction between a long induction period and an induction period of 3 months followed by a consolidation period with fairly intensive treatment of 1½ years; I believe it is all induction. There is some evidence that patients with nodular poorly differentiated lymphocytic lymphoma who achieve remission when maintained on therapy have a longer survival. On the other hand, several prospectively randomized studies have shown that if you let those patients relapse without maintenance and re-treat them after relapse they have a survival no different than that of a group continuously maintained. At our institute we are testing the effect of the methanol extraction residue of BCG as maintenance therapy in patients who achieve a complete remission. These patients are a useful population for study because with current programs they have a high rate of complete remission and yet a fairly high relapse rate. Other workers are studying the effectiveness of the immunostimulant levamisole as an adjuvant. Except for Sokol's study some years ago, which used bacillus Calmette-Guérin for maintenance treatment in a mixture of different types and stages of lymphomas, I know of no data which suggest immunotherapy is, as yet, of value in patients with lymphomas.

Dr. Rick: I would like to ask a clinicopathologic question. In the upper digestive tract we have great difficulty in distinguishing carcinomas from lymphomas, and when the same slides are sent to a number of hematopathologists some are identified as lymphomas and some as carcinomas. On the other hand, lesions arising in the head and neck region come back as reactive hyperplasias even though they act like lymphomas. I would like an opinion on these matters.

Dr. Glatstein: It is clear that a number of lesions in the tongue or nasopharynx are difficult to classify as either anaplastic carcinoma or lymphoma. Generally speaking, you should get second specimens of tissue, and sometimes electron microscopy helps. These lesions need aggressive local treatment and, in my opinion, these patients should have a lymphangiogram at least to look for subdiaphragmatic disease. It is common to see a tongue lesion treated locally and extending subdiaphragmatically 8–12 months later. Tissue from biopsy and laparotomy then shows diffuse histiocytic lymphoma.

Dr. Grossman: Some of the speakers have mentioned the impact of neutropenia and thrombocytopenia on their therapeutic regimens. In acute leukemia, experimental work has demonstrated that residual leukemia can inhibit bone marrow formation in vitro. Has this effect been studied in the lymphomas? It is possible that residual lymphoma is producing the neutropenia and thrombocytopenia and therefore its presence should not limit the therapeutic regimen.

Dr. DeVita: Patients with a higher volume of tumor have more leukopenia than those with a lower volume, though this is not easy to study in man. Animal data do suggest that residual tumor does impair bone marrow proliferation. In one study, using the CMF combination in breast cancer, patients who received therapy as an adjuvant in the postoperative period had less toxicity than patients who received therapy for metastatic disease.[3] This suggests that host characteristics and the volume of tumor are the factors which make the difference.

Dr. Gibbs: Is there any evidence to suggest that patients with an advanced stage of diffuse histiocytic lymphoma who achieve complete remission on chemotherapy should receive additional moderate-dose radiation therapy to areas of gross tumor involvement, particularly in areas that may be difficult to reach during second staging procedures?

Dr. Glatstein: The answer to your question involves another question. How confident are you of your complete remission? We have no good evidence at the present time that accurate restaging would show that such treatment is beneficial, although

[3]CMF = cyclophosphamide, methotrexate, and 5-fluorouracil.

personally I would like to think that it is. The studies I described today consisted of two or three cycles of chemotherapy, clinical restaging, then radiotherapy, then more chemotherapy; that is not the same as your program. It may well be that complete restaging would show that a minority of patients still fail even after a full course of aggressive, multi-agent chemotherapy.

Dr. DeVita: Dr. Rosenberg, would you recommend, on the basis of histopathologic information, that a subpopulation of patients with lymphoma should not be treated?

Dr. Rosenberg: I disagree with Dr. DeVita's interpretation that we selected out an unusual population. It is common to encounter elderly patients—by that I mean age 60 or over—who have nodular lymphomas, either mixed or lymphocytic, and have no symptoms. Indeed that is the most common presentation of these diseases. In that group the natural history is so good and evidence of convincing cure by any therapy is so scanty that initially they should receive no therapy. Over the next 5 or 10 years, however, almost all will require therapy, but the disease does not usually shorten their lives, at least in our series. Parenthetically, this group probably makes up more than two thirds of those you see with these histologies.

Dr. DeVita: A group of 35 patients were selected out of about 1000 seen at Stanford and untreated for reasons that did not relate to a specific protocol. I interpret the data differently because I have never seen an example—and nodular lymphomas are, in my view, no exception—of a population that did not benefit after achieving a long, durable, complete remission. I think you will find that this is true in Dr. Rosenberg's group, but because of the indolent nature of the illness, it does not appear in 5-year data.

Dr. Rosenberg: It is in that very group of patients that we don't get long, durable remissions.

Dr. DeVita: And you never will get these remissions if you don't treat them. However, we do see them at the National Cancer Institute even in patients with nodular poorly differentiated lymphocytic lymphoma but most certainly in those with nodular mixed histiocytic-lymphocytic lymphoma and nodular histiocytic lymphoma.

Audience: May we have a comment on the so-called benign pathologies such as angio-immunoblastic lymphadenopathy? I believe Dr. Rappaport put this into the malignant category. How do you categorize patients with angio-immunoblastic lymphadenopathy who die of their disease?

Dr. DeVita: Both Drs. Lukes and Rappaport have commented that morphologically these lesions look benign but clinically they are extremely malignant. Our experience is meager but these patients have not responded well to treatment, and the lesions behave as malignant disorders.

Dr. Seligmann: We are not in complete agreement with Drs. Lukes and Rappaport. There is a continuous sequence of events: morphologically some cases are probably malignant and the percentage is higher than stated in the Lukes paper. In some cases we have the impression that chemotherapy was of some value, but it's always difficult to tell. However, I believe the problem is more open than has been stated by some people in this country.

Summary of Symposium

Vincent T. DeVita [1,*]

The Symposium organizers asked that I take a moment to reflect on the data presented at this Symposium and make a few summary statements. In order to add some practicality to the obvious, I would like to comment on areas such as histopathology, staging, and therapy by contrasting the impact of data presented at this Symposium on both future clinical trials and the current practice of oncology. The reader will soon realize that although the conclusions in general reflect the consensus of the participants of this Symposium, my own personal biases have taken over when a clear consensus was not voiced; such is the nature of summaries.

Arguments still exist about the most useful histopathologic classification for the non-Hodgkin's lymphomas. My clinical colleagues appear to have concluded that the Rappaport classification is clinically significant and reproducible even though it may be scientifically inaccurate. Those most interested in immunologic investigation, on the other hand, prefer accuracy above all. Both views, of course, have merit. As Dr. Berard mentioned, the NCI is sponsoring a study of the leading histopathologic classifications which will examine their accuracy and reproducibility with reference to the total available clinical information, as well as their relevance to current immunologic data. The results, when available, may allow us to draw up a new and unique histopathologic classification that will provide clinical significance and reproducibility, as well as scientific accuracy, and also help us create a more effective staging classification.

In non-Hodgkin's lymphomas of all types we are dealing primarily with malignant lymphomas of B-cells. Dr. Seligmann emphasized the need for more data like those presented here by Dr. Bloomfield characterizing the immunologic characteristics of patients with lymphomas on treatment protocols. Unfortunately, although > 14 studies in the literature have now reported long-term survivors among patients with the diffuse histiocytic variety of the non-Hodgkin's lymphomas (DHL), we cannot yet categorize this population of patients by the exact cellular origin of their tumors, chiefly because they were treated before modern laboratory techniques for immunologic classification were available. Such data will be extremely important in explaining why some patients respond so well and others do not.

What are the implications of the histopathologic classification for clinical trials? All clinical trials, including those conducted by the clinical cooperative groups, are groping toward a common language, and the Rappaport classification appears to be the only system that can now be universally employed and preserve much needed reproducibility and prognostic information. It seems clear that the surface-marker studies should proceed in parallel with the use of the Rappaport classification, but we need not, at the present time, employ a system incorporating both if it means sacrificing reproducibility and prognostic value. I like Dr. Lukes' suggestion that we set up centers to provide surface-marker studies to support large clinical trials. This approach could provide the scientific accuracy now missing in some parts of the Rappaport classification.

The prompt application in the practice of medicine of advances derived from clinical research studies also requires a common language. There seems to be a consensus among clinicians that pathologists everywhere should adhere to the Rappaport classification.

Dr. Rosenberg told us good staging follows good pathology. We also learned that the Ann Arbor staging classification is imperfect when applied to non-Hodgkin's lymphoma. We are, however, all reluctant to change it because we are midway through a number of studies in which it forms the basis for a common staging language, and a clearly superior system is not immediately evident. All the staging data presented and reviewed, without exception, now show that most patients with non-Hodgkin's lymphoma have widespread disease at the time of diagnosis. Data from the NCI indicate that at least 60% of all patients with non-Hodgkin's lymphoma have disseminated disease at presentation. The lymphangiogram is a valuable test to predict the presence of tumor elsewhere. Seventy-five percent of patients with a positive lymphangio-

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gram will have disease outside lymph nodes in normal radiation fields and/or in the bone marrow and liver. The Stanford group has taken advantage of this information by adding the lateral decubitus ports to their radiation program to control mesenteric node spread, but it remains questionable that this approach will be useful in view of the high incidence of bone marrow and liver involvement in those patients with positive lymphangiograms.

The staging data undoubtedly reflect the biologic behavior of malignant lymphocytes. The small cleaved lymphocytes, we have heard, are motile and get into the peripheral blood in greater numbers than the larger transformed (more malignant) lymphocyte, and hence the ease in demonstrating widespread disease with simple techniques in patients with the nodular poorly differentiated lymphocytic variety of non-Hodgkin's lymphoma (NPDL).

What are the implications of the staging data for future clinical trials? The routine use of laparotomy is clearly not indicated; there appears to be no logical reason to subject patients in research studies to the increased risk of routine staging laparotomy. On the other hand, uniform staging is necessary because of the great benefit derived from common criteria. Uniform staging, we have been told, in addition to routine workup and studies, should include at least a bone marrow biopsy, a liver biopsy, and a lymphangiogram. Peritoneoscopy and other special tests seem to be optional, depending on clinical stage and local expertise. Laparotomy is probably best reserved for clinical stage I patients; in patients with stage I disease the relative roles of chemotherapy and radiotherapy are better established and more clearly separated, and knowledge of the precise stage, in these cases, leads to an "either/or" therapeutic decision.

The implications of accurate, uniform staging for private practice appear to be similar. Routine laparotomy appears not to be indicated, especially in view of the age of these patients and the information one can derive from simple tests. However, a uniform staging approach should be taken, as in research trials, and should also include a bone marrow biopsy, liver biopsy, and lymphangiogram.

In the management of these patients, all agree that the physician should use the team approach. No one should stage a patient with lymphoma unless he or she is working closely with those who will treat the patient. As Dr. Glatstein indicated, nothing is more distressing for a therapist than to have a patient referred from a surgeon who has performed an inadequate staging laparotomy because the surgeon did not know, or consider, the type of treatment to be offered to the patient. Patients have been subjected to considerable risk (nationwide, the morbidity from laparotomy in patients with non-Hodgkin's lymphoma is between 10% and 26% and mortality is twice that of patients with Hodgkin's disease) with ultimately no useful information being obtained.

We have also learned something about restaging. Twenty percent of patients who appear to be in complete remission have detectable disease when they are properly restaged. When those who appear to be free of disease after restaging continue without maintenance therapy, an additional 20% will relapse within 4 months. The Tucson group also reported a new finding of some interest. Lymphoma cells can be cultured after treatment from samples of morphologically normal marrows. Such an approach holds promise as the long sought after assay of small amounts of residual, but invisible, tumor.

In view of the risk of recurrence and our inability to detect small amounts of residual tumor with current, relatively crude, techniques, we seem to have little choice but to extend present treatment periods as the only reliable way to deal with microscopic residual disease. We need more clinical experiments evaluating staggered induction treatment times, such as are in progress in treatment trials in leukemia. Unfortunately, in the protocols presented at this Symposium, such trials were not much in evidence. Actually, one cooperative group is still evaluating remission status after 42 days of treatment; it seems very unlikely that this approach will be successful in accurately determining the true impact of a treatment program since no two patients should necessarily be expected to respond in the same way, or with the same speed, to any given treatment modality. Therefore, evaluation of remission status after a fixed time interval, regardless of duration, would not appear likely to be a true test of a therapeutic program. For the same reason, it is unlikely that a fixed number of cycles of treatment can be recommended for all patients even with similar histologic subtypes; clinical trials employing flexible induction periods deserve greater emphasis. Of course, we also shall need uniform restaging, and the data presented at this Symposium suggest we should at least repeat all the tests that were positive during the pretreatment staging, that is, everything short of a laparotomy.

Physicians in the community should also avoid adopting a fixed treatment schedule, even for older programs, and should not shy away from more prolonged treatment schedules even if patients remit early. Practicing physicians should be encouraged to restage, particularly before deciding to discontinue treatment in someone who is otherwise doing well, often a difficult decision in private practice in the absence of a protocol.

Again and again we have heard that patients with nodular lymphomas have a good overall prognosis. For many years the median survival for patients with advanced disease has been known to exceed 6 years except for a few studies (some reported here) where the survival is so much less than, say, that reported from Stanford or the NCI, that a selection factor is clearly suggested. Since reports from the former groups tend to reflect negatively on therapeutic programs that appear beneficial in most studies, the discrepancy causes confusion for the practicing physicians.

We have also learned that no single drug combination is superior in advanced NPDL, the most common histologic variety. Single-agent therapy (and indeed no therapy, at least for a time, says the Stanford group) may still have a role here, a role that has been de-emphasized in recent years, although it is difficult to draw conclusions from data derived from only a selected 35 patients (out of a denominator of nearly 1000). In a controlled trial at Stanford, the complete remission rates for CVP versus chlorambucil were 83% and 65% respectively, with speed of remission induction superior for CVP.[2] Given the NCI data suggesting that complete remissions are always beneficial and all the data suggesting that the simpler combinations are not particularly risky to use, it appears reasonable to continue to rely on drug combinations for induction treatment.

It is of some importance that, in contrast to NPDL, the patients with the nodular mixed (NML) and the nodular histiocytic (NHL) varieties of lymphomas, in their advanced stages, have a high percentage of durable complete remissions when treated with some of the older combinations such as MOPP or C-MOPP.[3] Dr. Young reported a 75% complete remission rate and few relapses over 9 years of followup. Thus another variety of patients, like those with diffuse histiocytic lymphoma (DHL), may well be curable in their advanced stages with drugs alone. This observation should again raise the question of the utility of drugs in these varieties of lymphomas in patients with earlier stages of tumor with or without adjuvant radiotherapy.

Dr. Bonadonna has presented some disturbing new data. When used in sequence, two proven, noncross-resistant drug combinations are providing no more benefit in terms of complete remission rate than when each is used alone. Part of the explanation may be that one combination may affect the way the tumor can respond to the second.

All investigators seem to agree that diffuse well-differentiated lymphocytic lymphoma (DWDL) behaves much like chronic lymphocytic leukemia and probably should be treated like that disease. Unfortunately, the admixture of this group of patients with the other lymphomas, in some studies, confused the data presented by a number of investigators: for example, 22% of the patients in the Acute Leukemia Group B studies, reported at this Symposium, have DWDL. The less well-differentiated diffuse lymphomas, on the other hand, do poorly with radiation therapy alone. It has been stressed that we must separate the therapeutic results for stage I and II patients because each stage has a different natural history. Stage I patients tend to have a disease-free survival of 50%–60%, and occasionally higher, with radiation treatment alone; stage II patients consistently have < 30% disease-free survival in most large series, including the series from Stanford.

In patients with DHL it is extremely important to achieve a complete remission with the initial treatment attempt. Complete response rates reported at this Symposium and elsewhere vary between 30% and 88% in patients with stage III or IV disease. These complete remissions are reported to endure in 25%–82% of patients; on the average, 25%–45% of the entire treated population survive, relapse-free, for periods extending in some studies to 10 or 11 years. Data from the NCI suggest that the differences in response rates and durability of response among different series are in part explained by the varying sites of tumor involvement in the studies reported; thus, patients with gastrointestinal and bone marrow involvement have the worst prognosis. In all, some eight drug combinations (CHOP, HOP, C-MOPP, BACOP, COMA, MEV, CAT, and B-COP) now show evidence that a small, but significant, population of patients with stage III and IV disease achieve long-term survival.[4] All seemed to agree, as Dr. McKelvey reiterated in his review of the literature, that the shape of the relapse-free survival curve for patients with DHL

[2]CVP = cyclophosphamide, vincristine, and prednisone.

[3]MOPP = mechlorethamine, vincristine, prednisoné, and procarbazine.

C-MOPP = cyclophosphamide, vincristine, prednisone, and procarbazine.

[4]CHOP = cyclophosphamide, adriamycin, vincristine, and prednisone.

HOP = adriamycin, vincristine, and prednisone.

BACOP = bleomycin, adriamycin, CCNU, vincristine, and prednisone.

COMA = cyclophosphamide, vincristine, methotrexate (plus citrovorum factor rescue), and cytosine arabinoside.

MEV = mechlorethamine, cyclophosphamide, and vincristine.

CAT = cytosine arabinoside, adriamycin, and 6-thioguanine.

B-COP = BCNU, cyclophosphamide, vincristine, and prednisone.

strongly suggests these patients are cured with drugs alone.

Not much was said at this meeting about immunotherapy, which is a bit surprising. Although many studies evaluating immunotherapy are in progress there are, as yet, no hard data. We need a new, more effective combination of drugs for patients with NPDL; CVP is useful but not good enough. The notion that aggressive treatment is of no value in this group is unproved and could be counterproductive if it impedes the design of further trials. Results in patients with advanced NPDL at the NCI, presented by Dr. Young, in contrast to the data reviewed by Dr. McKelvey, are beginning to show a small tail on the survival curve of CVP-treated patients with stage III and IV disease that suggests about 20% of the patients may have a diminishing risk of relapse (cure?). Dr. Glatstein noted that this is roughly where the curve falls with radiotherapy as well, but his results were in stage III patients only. The problem with this variety of lymphoma is that because of the relatively good prognosis, long periods of time are required to evaluate the effect of therapy and time blurs therapeutic focus.

We have learned, again, that local irradiation therapy controls local tumor but fails to cure most patients because of microscopic disease outside radiation ports. Data from Stanford suggest that involved-field radiotherapy is as good as total-nodal irradiation in patients with localized non-Hodgkin's lymphoma.

I believe enough data are available to support the hypothesis that chemotherapy *could be* the treatment of choice for patients with localized DHL, a hypothesis which demands clinical trial. Thus, some of us disagree with Dr. Bush when he said that because radiotherapy produces a 75% response in the treatment field and chemotherapy produces only a 50% complete response rate (*in the whole patient*) we should not question the use of radiotherapy as the primary treatment in well-staged patients with localized tumor. The relapse-free survival in patients with stage III or IV disease, treated with drugs alone, in studies mentioned above, approximates closely the disease-free survival achievable with radiotherapy alone in patients with stage II DHL. We need comparative trials of radiotherapy and the best chemotherapy in stage I and II DHL, DPDL, NML, NHL, and diffuse undifferentiated lymphoma (DUL). Such a study could compare involved-field radiotherapy with one of the combinations shown to produce durable complete remissions to both radiotherapy and chemotherapy used together.

A disturbing chauvinism is apparent in the design of therapeutic trials, particularly those developed in large cooperative groups. Investigators have a tendency to use combinations they or their group developed as the basis for new studies, even when the literature supports the view that other drug combinations are doing better. When we do this we lose our capacity to leap-frog over each other's data. This trend assumes more importance in combined modality studies in patients with early disease. If one is going to do an adjuvant study, he or she should select a drug combination of maximum proved benefit as determined in patients with advanced disease; thus, for chemotherapy trials involving stage I and II patients, it is most appropriate to choose one of the eight combinations mentioned above, and other equivalent ones that come along, to minimize the risk of designing and using a new but perhaps less effective drug combination in patients with "invisible disease" where a negative effect is not readily apparent. Studies testing the hypothesis of the usefulness of chemotherapy in patients with stage I and II disease, when developed, should produce answers quickly, in about 2 years, because as a group the large cell lymphomas are aggressive diseases and relapse usually occurs within the first 2 years even in patients with early tumors. Many studies in progress are examining the effectiveness of new combinations, but few are doing so in comparison to the reference standards (the eight combinations listed above)—a hazardous way to do clinical research, in my view, and an approach which will not make it easier for clinicians to select "the best" combinations for adjuvant studies.

The doctor in clinical practice would be well advised to take part in any well-designed study examining the relationship of staging to therapy. However, if he or she has to make the therapeutic decision in the absence of a clinical trial, I would offer the following recommendations based on data presented at this Symposium. Patients with stage I or II DWDL may be treated by radiation therapy alone; these patients will remain free of disease for a long time, but all will eventually develop recurrences. Patients who present with stage III or IV DWDL, or in relapse after radiotherapy, can be treated with chlorambucil alone. I have seen no data suggesting that any other approach is better. Total-body radiation is an alternative as second-line treatment. The drug combination programs reported here appear too aggressive for this disease.

For patients with stage I and II disease of the other histologic types, particularly the nodular varieties, involved-field radiation therapy should still be the treatment of choice in practice as a standard therapy. Whether physicians add chemotherapy to

radiotherapy in these patients, as suggested above for the research trials, depends on their own biases, but at this time it need not be considered a necessary concomitant of therapy until more information is available from clinical trials.

In stage III or IV NPDL, combination chemotherapy, in my view, is easier to administer than chlorambucil and still more likely to achieve the desired effect, a complete remission. Opinions vary on this point. However, the continuous use of chlorambucil is not as benign as it appears; the drug produces a persistent, prolonged pancytopenia in patients who are treated for > 1 or 2 years; we do not encounter that type of complication with intermittent CVP.

For patients with stage III or IV NML, NHL, DHL, and DUL, practitioners would do well to select a treatment from the group of known effective combinations mentioned above. Unless a physician is involved in a clinical trial, it is hazardous to design an ad hoc combination to treat a single patient, or a few patients, and risk a negative effect when enough information on drug combinations is available to allow a selection based on age and condition of the patient and availability of drugs. One should not assume that because three drugs are active in one schedule those same three drugs, used in a way *that may be more convenient* to the doctor or patient, will give as good or better clinical results.

I have one further comment about the use of combined modalities. At the present time, we have very little information about the interaction of radiation therapy and drugs. In fact, some data suggest that an active drug can be rendered inactive by irradiating the tumor beforehand. Thus, we do not know the safest and most effective sequence in which to use chemotherapy and radiotherapy. A number of studies are now under way examining these important questions, but in the meantime we should not assume an invariably additive effect when radiation is added to chemotherapy or vice versa.

In my view, this has been an extremely interesting and useful Symposium. It has combined some new information with re-examination of older data and has provided a good synthesis of recent progress in a rapidly moving field. While in the last 5 years this field of investigation has seen dramatic changes, I believe the existing data point out many other avenues of potential fruitful investigation that in the next 5 or 10 years should bring even greater progress.

ANNOUNCEMENTS

Seminar on Malignant Bone Tumors

Eastern Maine Medical Center, Bangor, Maine, October 7–8, 1977

This is a multidisciplinary seminar which is sponsored by Dahl-Chase Pathology Associates, the American Cancer Society (Maine Division), Sidney Farber Cancer Center, and Eastern Maine Medical Center.

The faculty consists of: Lent C. Johnson, MD (Armed Forces Institute of Pathology, Washington DC), Hugh G. Watts, MD (Children's Hospital Medical Center, Boston, Mass), Norman Jaffe, MD (Sidney Farber Cancer Center, Boston, Mass), Demetrius G. Traggis, MD (Eastern Maine Medical Center, Bangor, Me), J. Robert Cassady, MD (Harvard Medical School, Boston, Mass), and Robert H. Wilkinson, MD (Children's Hospital Medical Center, Boston, Mass).

The registration fee is $50.00 for practicing physicians and $25.00 for residents. *For further information contact* Robert H. Brown, MD, Seminar Chairman, Eastern Maine Medical Center, Bangor, Me 04401.

Seminars in Oncology at Roswell Park Memorial Institute

Buffalo, New York

There will be a seminar(s) on "Anesthesia in the Cancer Patient—Blood Pressure Problems" on November 10, 1977, organized by the Department of Anesthesia of the Roswell Park Memorial Institute. The chairperson is Dr. Raymond Trudnowski.

There is a $10.00 registration fee. *For further information contact:* Ms. Claudia Lee, Cancer Control, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263.

US National Committee for the International Union Against Cancer Travel Awards

The US National Committee for the International Union Against Cancer (UICC) is sponsoring a travel grant program to benefit US scientists who can not attend the XII International Cancer Congress in Buenos Aires, Argentina, to be held October 5–11, 1978, without such assistance.

There are two categories of travel awards that will be available: (I) invited participants of conferences and symposia, and (II) presentors of proffered papers (free communications). The number of grants in category II will be limited. Those eligible for awards in category II are qualified scientists who are citizens or permanent residents of the US. Each applicant will be judged on the merit of his contribution to the Congress, considering his training, experience, and potential, as well as a reasonable representation of age groups. The application must be approved by an appropriate official of the applicant's institution. *Final approval of the travel award cannot be made until the US National Committee receives official verification of acceptance of the paper by the XII Cancer Congress Program Committee.* Both categories of grants will ordinarily be limited to economy roundtrip air fare plus $150. The deadline for receipt of applications is February 1, 1978.

***Requests for application forms should be addressed to:* US National Committee for the UICC, Division of Medical Sciences, National Research Council, 2101 Constitution Ave, NW, Washington, DC 20418.**

Change in Training Requirements for the American Board of Internal Medicine's Subspecialty Examinations

The American Board of Internal Medicine has announced a significant change in policy regarding its training requirements. This change will affect physicians desiring admission to a subspecialty examination who began their residency training in *internal medicine* before June 1, 1970. At present, these physicians are considered to have met the training requirements for admission to a subspecialty examination after completing 1 year of

acceptable training in the subspecialty. If once informed of admission to a subspecialty examination, these physicians *will continue* to be considered to have fulfilled the Board's training requirements in that subspecialty. Beginning with the subspecialty examination offered in 1981, however, *all physicians* not previously admitted to an examination will be required to meet the same training requirements which apply to physicians beginning their residency training after June 1, 1970. These requirements currently involve 2 full years of acceptable training in the subspecialty. *A complete description of the Board's policies and procedures may be obtained by directing a written request to:* American Board of Internal Medicine, 3930 Chestnut Street, Philadelphia, PA 19104. (The next examination in Medical Oncology will be offered in June 1979.)

Postgraduate Course in Neuro-Oncology

New York, New York, October 6–8, 1977

The Memorial Sloan-Kettering Cancer Center's Department of Neurology announces a postgraduate course in neuro-oncology to be held October 6–8, 1977, at Memorial Hospital, 1275 York Ave, New York, NY. The course will review metastatic and non-metastatic neurologic complications of systemic cancer as well as primary central nervous system tumors. The diagnosis of these disorders in adults and children and their treatment by conventional and experimental methods will be covered. Specific topics include: clinical evaluation of patients with primary and metastatic central nervous system tumors, conventional and experimental radiation therapy, chemotherapy, and immunotherapy of metastatic and primary brain tumors, complications of therapy, the role of surgery in the treatment of patients with metastatic and primary tumors, non-metastatic complications of systemic cancer, and evaluation and treatment of patients with pain resulting from cancer.

The faculty includes Drs. Jeffrey C. Allen, Norman L. Chernik, Michael D. F. Deck, Kathleen M. Foley, Joseph H. Galicich, Robert A. Good, Rene C. Mastrovito, Jerome B. Posner, Richard W. Price, David A. Rottenberg, William R. Shapiro, Lewis Thomas, and Dean F. Young.

For further information contact: Dr. Jerome B. Posner, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021 (phone: 212-794-7047).

CORRECTION

The following changes should be made in the article "Advances in Small Cell Bronchogenic Carcinoma" by Paul A. Bunn, Jr, et al, which appeared in the May/June 1977 issue. In table 5 (page 338), line 9, the schedule for cyclophosphamide should be *q3wks* rather than q4wks as shown. Also, the doses of methotrexate are given *twice a week* in all four combinations.

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